Single Technology Appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY 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. **Company submission** from Pfizer
   a. **Company submission addendum**

2. **Company summary of information for patients (SIP)** from Pfizer

3. **Clarification questions and company responses (main)**
   a. Response to question A6
   b. Response to question B2
   c. Response to question B17

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

5. **Expert personal perspectives** from:
   a. Suneil Jain, professor of clinical oncology – clinical expert nominated by Pfizer and British UroOncology Group
   b. Holly Knight – patient expert nominated by Prostate Cancer UK (*see item 4a)

6. **External Assessment Report** prepared by PenTAG
   a. Original cost comparison report (for information)

7. **External Assessment Report – factual accuracy check**

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

Single technology appraisal: cost comparison

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Document B

Company evidence submission

August 2024

File name	Version	Contains confidential information	Date
ID4004_Talazoparib for mCRPC_Document B_14Aug24_[noCON]	Final	No	14 August 2024

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full marketing authorisation for the following indication: talazoparib with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.[1]

The company proposes that this appraisal is considered under the National Institute for Health and Care Excellence (NICE) single technology appraisal cost comparison process. The NICE manual and user guide for the cost comparison company evidence submission template (2022) state that a cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published guidance for the same indication.[2,3]

Olaparib with abiraterone (and prednisone or prednisolone), hereafter referred to as "olaparib with abiraterone", is the first combination therapy approved and recommended for mCRPC (TA951) and is of the same combination class technology as talazoparib with enzalutamide; it is therefore the only relevant comparator for this cost comparison appraisal.[4,5] The wording of the recommendation in TA951 is: "Olaparib with abiraterone and prednisone or prednisolone is recommended, within its marketing authorisation, as an option for untreated hormone-relapsed metastatic prostate cancer in adults who cannot have or do not want chemotherapy".[5] As described in **Section B.1.3.1**, mCRPC is also known as metastatic hormone-relapsed or hormone-refractory prostate cancer, so talazoparib with enzalutamide is for the same indication as TA951.

The company is pursuing the same positioning and recommendation as olaparib with abiraterone in TA951,[5] for the following reasons:

- **Mechanism of action**: Talazoparib and olaparib are in the same drug class of poly adenosine diphosphate ribose polymerase (PARP) inhibitors. PARP

inhibitors prevent DNA repair, leading to the accumulation of DNA damage and cell death through synthetic lethality. Similarly, enzalutamide and abiraterone are both new hormonal agents (NHAs) that inhibit the androgen receptor pathway with similar mechanisms of action. The External Assessment Group (EAG) in TA951 considered enzalutamide and abiraterone to be “equally relevant”, with patients eligible to receive either treatment, and the choice based on relevant comorbidities or clinician preference.[5]

- **Similar health benefits**: A network meta-analysis (NMA) was conducted in July 2024 to estimate the relative efficacy of talazoparib with enzalutamide (TALAPRO-2 study) versus other first-line treatments for patients with mCRPC, including olaparib with abiraterone (PROpel study). The results from the NMA showed that talazoparib with enzalutamide is associated with [redacted] versus olaparib with abiraterone for key efficacy outcomes, including radiographic progression-free survival (rPFS), overall survival (OS), and time to prostate-specific antigen (PSA) progression, PSA response, and objective response rate (ORR) (see **Section B.3.9.3** for further details).[6] Additionally, the safety profiles of talazoparib with enzalutamide and olaparib with abiraterone are comparable (see **Section B.3.11** for further details).

- **Same target population**: As explained above, the marketing authorisations of each combination are comparable. Furthermore, UK clinical experts consulted in August 2024 confirmed that talazoparib with enzalutamide is expected to be used in the same population as olaparib with abiraterone, given their similar mechanism of action and clinical efficacy.[7]

- **Lower costs**: A cost comparison analysis has been conducted to determine the expected cost difference in clinical practice between talazoparib with enzalutamide and olaparib with abiraterone for the treatment of patients with mCRPC for whom chemotherapy is not clinically indicated. The analysis was conducted over a lifetime horizon from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) in England and Wales (see **Section B.4** for further details). Talazoparib with enzalutamide was

estimated to generate cost savings compared to olaparib with abiraterone over the model time horizon.

Given the above, talazoparib with enzalutamide provides similar or greater health benefits at a lower cost than olaparib with abiraterone, and offers an additional treatment option for patients with mCRPC in whom chemotherapy is not clinically indicated. Full details of the decision problem addressed in the submission are summarised in **Table 1**.

Table 1: Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated	In line with scope	N/A
Intervention	Talazoparib in combination with enzalutamide	In line with scope	N/A
Comparator(s)	• Enzalutamide • Abiraterone with prednisone or prednisolone • Olaparib with abiraterone (and prednisone or prednisolone)	Olaparib with abiraterone	Olaparib with abiraterone represents the only relevant comparator for this cost comparison submission. Although enzalutamide monotherapy and abiraterone monotherapy are also in the same position in the treatment pathway as talazoparib with enzalutamide and olaparib with abiraterone, they are not relevant to this cost comparison appraisal because olaparib with abiraterone was shown to be cost-effective against both enzalutamide monotherapy and abiraterone monotherapy in TA951.[4] Given that talazoparib with enzalutamide provides similar or greater health benefits at similar or lower costs than olaparib with abiraterone, a comparison versus enzalutamide and abiraterone is therefore not required.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate	In line with scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Adverse effects of treatment • Health-related quality of life		
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.[2] 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.	In line with scope	This submission presents a cost comparison of talazoparib with enzalutamide versus olaparib with abiraterone (see **Section B.4** for details). As talazoparib with enzalutamide is licensed for all eligible adult patients with mCRPC in whom chemotherapy is not clinically indicated, regardless of biomarker status, no specific genetic testing is required. There will be no further monitoring requirements beyond current clinical practice.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The economic modelling should include the cost associated with diagnostic testing for people with hormone-relapsed metastatic prostate cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		

Subgroups to be considered	If the evidence allows, the following subgroups should be considered:
	
	• HRR status including:
	  ○ BRCA1 and BRCA2
	  ○ ATM gene.
		None	According to NICE guidance on cost comparisons,[2] results of subgroup analyses are not required if the technology provides similar or better health benefits at a similar or lower price than the intervention in the full population. As this is the case for the comparison of talazoparib with enzalutamide versus olaparib with abiraterone, subgroup analyses are not presented.
			.

Abbreviations ATM – Ataxia-telangiectasia mutated; BRCA – Breast cancer susceptibility gene; HRR – Homologous recombination repair; mCRPC – Metastatic castration-resistant prostate cancer; N/A – Not applicable; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; TA – Technology appraisal

B.1.2 Description of the technology being evaluated

Table 2 summarises the technology being appraised in this submission. The Summary of Product Characteristics (SmPC) can be found in **Appendix C**.

Table 2: Technology being evaluated

UK approved name and brand name	Talazoparib (Talzenna®) with enzalutamide (Xtandi®)
Mechanism of action	Talazoparib is a potent oral small molecule inhibitor of PARP enzymes. Talazoparib exerts its cytotoxic effects via the inhibition of PARP1 and PARP2 enzymatic activity and PARP trapping.[8–11] Enzalutamide is a NHA that inhibits the androgen receptor signalling pathway.[12] There is a proposed combined effect when PARP inhibition and NHAs are used in combination, where AR blockade and sensitivity to PARP inhibition may be synergistic.[12] Suppression of HRR genes (including BRCA1) increases the sensitivity of tumour cells to PARP inhibition. Clinical resistance to AR blockade is sometimes associated with co-deletion of RB1 and BRCA2, which in turn is associated with sensitivity to PARP inhibition.[13]
Marketing authorisation/ CE mark status	Talazoparib received full marketing authorisation from the EMA in 2019 for the treatment of adult patients with germline BRCA1/2 mutations who have HER2-negative locally advanced or metastatic breast cancer.[14,15] In January 2021, talazoparib received an MHRA grandfathering approval for the treatment of prostate malignant neoplasms.[16] In November 2023, the CHMP adopted a positive opinion recommending an extension of therapeutic indication for talazoparib in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. Full marketing authorisation was granted by the EMA in January 2024.[14,15]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	According to the SmPC[14], the licensed indications for talazoparib are: • Prostate cancer: "Talzenna is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated." • Breast cancer: "Talzenna is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with HR-positive breast cancer should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy."

Method of administration and dosage	The recommended dose is 0.5 mg talazoparib in combination with 160 mg enzalutamide once daily. Patients should be treated until disease progression or unacceptable toxicity occurs.[14] Talazoparib is for oral use. It can be taken with or without food.
Additional tests or investigations	As talazoparib with enzalutamide is licensed for all eligible adult patients with mCRPC in whom chemotherapy is not clinically indicated, regardless of biomarker status, no specific genetic testing is required. There will be no further monitoring requirements beyond current clinical practice.
List price and average cost of a course of treatment	Talazoparib is available at a list price of £1,655.00 for a pack of 30 x 0.10 mg capsules and £1,655.00 for a pack of 30 x 0.25 mg capsules. Enzalutamide is available at a list price of £2,734.67 for a pack of 112 x 40 mg tablets. The average monthly cost of treatment with talazoparib with enzalutamide in the indication relevant to this appraisal is £6,240.00 (list price) based on the dose and posology specified in the respective SmPCs.
Patient access scheme/commercial arrangement (if applicable)	A simple PAS discount of [redacted] is available for talazoparib, resulting in a net price of [redacted] for a pack of 30 x 0.25 mg capsules.

Abbreviations: AR – Androgen receptor; BRCA – Breast cancer susceptibility gene; CE – European Conformity; CHMP – Committee for Medicinal Products for Human Use; EMA – European Medicines Agency; HER – Human epidermal receptor growth factor; HR – Hormone receptor; HRR – Homologous recombination repair; mCRPC – Metastatic castration-resistant prostate cancer; MHRA – Medicines and Healthcare products Regulatory Agency; NHA – New generation hormonal agent; PARP – Poly ADP ribose polymerases; PAS – Patient-access scheme; RB – Retinoblastoma; SmPC – Summary of product characteristic; UK – United Kingdom

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Prostate cancer is the most common and most frequently diagnosed form of cancer in men in the United Kingdom (UK).[17,18] There are approximately 55,100 new prostate cancer cases annually in the UK, of which 13% present with metastatic disease at diagnosis.[18,19] Approximately 12,000 prostate cancer deaths are recorded annually in the UK, making prostate cancer the second most common cause of cancer death in males in the UK.[18]

NICE Clinical Guideline 131 (NG131; published in May 2019, updated in December 2021) refers to the stages of prostate cancer as: localised disease, locally advanced disease, and metastatic disease, where the cancer has spread to distant sites in the

body.[20] Further subcategories – based on response to androgen deprivation therapy (ADT) – include hormone-sensitive prostate cancer (HSPC), which is sensitive to ADT, and castration-resistant prostate cancer (CRPC; also known as hormone-relapsed or hormone-refractory prostate cancer), which is no longer sensitive to ADT. Metastatic disease that no longer responds to ADT is referred to as mCRPC.

When diagnosed at an early stage, prostate cancer is treatable and well-managed using conventional interventions, including hormone therapy (e.g., ADT, NHA); however, advanced stages of disease are incurable.[21–23] Most patients develop mCRPC following progression from earlier stages of the disease, with approximately 65–73% progressing from metastatic castration-sensitive prostate cancer (mCSPC), and 26–35% progressing from non-metastatic castration-resistant prostate cancer (nmCRPC). In the UK, the estimated prevalence of mCRPC is 1.2% among overall prostate cancer cases,[24] and the estimated incidence rate is approximately 78–85 per 100,000 population.[17,18]

Unlike localised prostate cancer, which has a positive prognosis with 5-year survival rates of 99.6%,[25] the prognosis for mCRPC remains poor, with a 5-year survival rate for patients with metastases of 30%.[26,27] Although several real-world studies suggest survival outcomes have improved with the introduction of new systemic therapies, median survival remains less than 4 years.[26–30] Patients with mCRPC report a high symptom burden, including fatigue, pain, urinary frequency,[31] and substantial health-related quality of life (HRQoL) decline.[32] Additionally, patients with bone metastases experience considerable morbidity burden from skeletal-related events (SREs), which include pathological fractures, spinal cord compression, severe pain requiring radiotherapy, or surgery for bone.[33,34] As mCRPC is incurable and has a poor prognosis, the main goal of treatment is to prolong survival and maintain HRQoL.

B.1.3.2 Clinical pathway of care

In the UK, treatment guidelines for the management of prostate cancer are available from NICE (refer to NG131) and the European Society of Medical Oncology (ESMO).[20,23] For patients with hormone-sensitive non-metastatic prostate cancer, the mainstay of treatment is ADT or radical therapy (surgery and radiotherapy).[20] Following disease progression to hormone-relapsed non-metastatic prostate cancer,

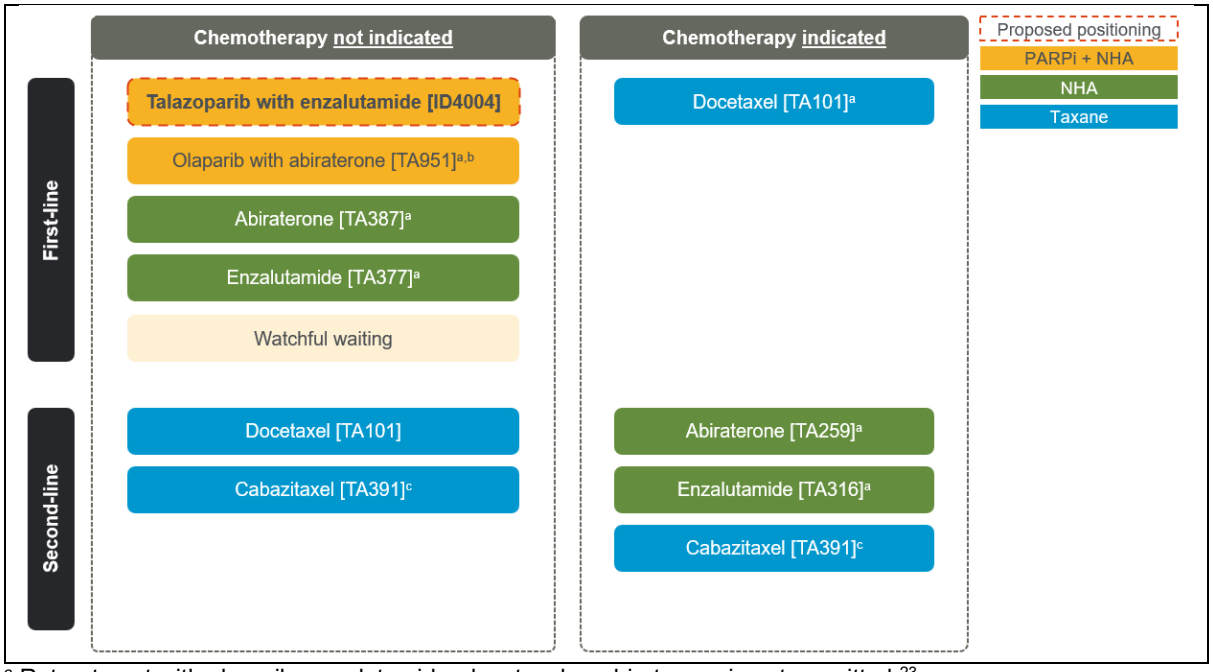
treatment with ADT continues either alone or, for patients at high risk of metastases, in combination with apalutamide (TA740) or darolutamide (TA660).[20,35,36] For patients with mHSPC, treatment options include ADT alone or in combination with docetaxel, enzalutamide (TA712), apalutamide (TA741), or darolutamide with docetaxel (TA903).[20,37–39]

For patients with mCRPC, docetaxel is recommended where chemotherapy is indicated and Karnofsky performance status score is 60% or higher (TA101).[40] Following disease progression on docetaxel, treatment options include systemic therapy with abiraterone (TA259) or enzalutamide (TA316) if not previously received, or cabazitaxel (TA391).[41–43] First-line treatment options for mCRPC patients for whom chemotherapy is not indicated include enzalutamide (TA377), abiraterone (TA387), and, since February 2024, olaparib with abiraterone (TA951).[44–46]

The licensed indication for talazoparib with enzalutamide is for the treatment of adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated.[14] As such, the proposed positioning of talazoparib with enzalutamide is alongside olaparib with abiraterone, enzalutamide, abiraterone and cabazitaxel as a first-line treatment option for mCRPC.

A summary of the clinical pathway of care and position of talazoparib with enzalutamide is presented in **Figure 1**.

Figure 1: Proposed clinical pathway of care and position for mCRPC



[a] Retreatment with olaparib, enzalutamide, docetaxel or abiraterone is not permitted.[23]
[b] Olaparib monotherapy is recommended for patients with mCRPC and BRCA1/2 mutations (germline and/or somatic) after progression on NHA (TA887).[47]
[c] Cabazitaxel requires previous docetaxel, ECOG 0/1 and does not cover those who had docetaxel then abiraterone or enzalutamide (TA391).[43] Cabazitaxel is also a treatment option in patients ineligible for chemotherapy.[43]
Abbreviations: BRCA – Breast cancer gene; ECOG – Eastern Cooperative Oncology Group; mCRPC – Metastatic castration-resistant prostate cancer; NHA – New hormonal agent; PARPi – Poly adenosine diphosphate ribose polymerase inhibitor; TA – Technology appraisal

For patients eligible for a PARP inhibitor/NHA combination, the only option at present is a combination containing abiraterone. Clinicians have a number of NHA options in mCRPC, including both enzalutamide and abiraterone, and the choice of the most appropriate NHA for a particular patient is multifactorial.[7] Where the NHA of choice in mCRPC is not abiraterone, there is currently no option available for these patients to receive PARP inhibitor/NHA combination therapy, creating a potential inequality in access. In addition, olaparib with abiraterone is contraindicated for some patients due to the associated risks of cardiotoxicity and challenges associated with steroid-exposure, such as uncontrolled diabetes, infection, osteoporosis, osteopenia, and gastro-intestinal bleeding. For those reasons, UK clinical experts noted that there is a need for new treatments to ensure they have a range of effective options to treat patients.[7]

Although talazoparib with enzalutamide is positioned in the same place in the treatment pathway as olaparib with abiraterone, enzalutamide, and abiraterone, the

cost-effectiveness of olaparib with abiraterone was demonstrated against both enzalutamide and abiraterone in TA951.[46] Given that talazoparib with enzalutamide provides similar or greater health benefits at similar or lower costs than olaparib with abiraterone (**Sections B.3** and **Section B.4**), a comparison versus enzalutamide and abiraterone is therefore not required, and olaparib with abiraterone represents the only relevant comparator for this cost comparison submission. In line with UK clinical expert opinion, talazoparib with enzalutamide is considered to have similar clinical efficacy and safety to olaparib with abiraterone, with treatment choice dependent on clinical preference and patient profile.[7]

B.1.4 Equality considerations

Around 1 in 6 men develop prostate cancer and this disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer.[18,48] A broader range of treatment options will help to provide broader access and equity in outcomes for patients of all ethnicities.

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

As noted in **Section B.1.3.2**, olaparib with abiraterone represents the only relevant comparator for this appraisal. Olaparib with abiraterone was found to be cost-effective versus enzalutamide and abiraterone with prednisone or prednisolone in TA951.[46] The key clinical outcomes and measures used in the cost-effectiveness analysis in TA951, as well as the committee's preferred assumptions and uncertainties, are presented in **Table 3**.

Table 3: Clinical outcomes and measures appraised in NICE TA951 (olaparib with abiraterone)

Outcome	Measurement scale	Use in cost-effectiveness modelling	Impact on ICER	Committee's preferred assumptions	Uncertainties (if applicable)
OS	Time from randomisation to death from any cause.	Independent parametric curves were fitted to the OS data from the PROpel RCT for olaparib with abiraterone and for placebo with abiraterone. Generalised gamma distribution was used to extrapolate OS for both olaparib with abiraterone and placebo with abiraterone. Based on the results of the NMA, an equivalent hazard ratio (HR=1) for enzalutamide compared to placebo with abiraterone was applied.	In the comparison of olaparib plus abiraterone versus enzalutamide: High (OS hazard ratios) In the comparison versus abiraterone: Low	Despite the EAGs questioning of the validity of the NMA due to substantial heterogeneity between the included trials, the committee acknowledged the limitations of the EAG's meta-analysis and agreed with the assumption of clinical equivalence between enzalutamide and abiraterone. The committee preferred the EAGs fully incremental analysis format to the company's pairwise analysis. The generalised gamma curve fit was questioned against the log-logistic curve, but the committee agreed with the clinical input that generalised gamma was more suitable.	Though the committee agreed with the company, in the final analysis they also considered the EAGs preferred OS HR (0.84) for the relative efficacy of abiraterone and enzalutamide.
rPFS	Investigator-assessed RECIST 1.1 criteria for soft tissue and the PCWG-3 criteria for bone.	Independent parametric curves were fitted to the rPFS data from PROpel for olaparib with abiraterone and for placebo with abiraterone. Based on the results of the NMA for OS, and an assumption that there is no difference in efficacy between abiraterone and enzalutamide in terms of either	In the comparison of olaparib plus abiraterone versus enzalutamide: Low In the comparison versus abiraterone: Low	No PFS NMA was conducted, but the committee agreed with the assumption of clinical equivalence between enzalutamide and abiraterone (see OS row for details).	None

Outcome	Measurement scale	Use in cost-effectiveness modelling	Impact on ICER	Committee's preferred assumptions	Uncertainties (if applicable)
		rPFS or OS, an equivalent hazard ratio (HR=1) for enzalutamide compared to placebo with abiraterone was applied. Generalised gamma distributions were used for the extrapolation of rPFS outcomes for both arms.			
TTD	Time from randomisation to discontinuation.	TTDA and TTD were modelled independently (using an equivalent methodology to OS and rPFS) using data from the PROpel RCT for both olaparib with abiraterone and placebo with abiraterone. Based on the unavailability of TTD data for enzalutamide, and the assumption of equivalence from the NMA, an equivalent hazard ratio (HR=1) was applied for enzalutamide versus placebo with abiraterone for TTDA and TTD. Generalised gamma distributions were used for extrapolation of TTD outcomes for both arms.	In the comparison of olaparib plus abiraterone versus enzalutamide: High (time on treatment for enzalutamide) In the comparison versus abiraterone: Low	None	None
AEs	Incidence of CTCAEs grade ≥3.	Prevalence and duration of grade ≥3 CTCAEs reported in ≥5% were sourced from the PROpel RCT (for olaparib with	In the comparison of olaparib plus	None	None

Outcome	Measurement scale	Use in cost-effectiveness modelling	Impact on ICER	Committee's preferred assumptions	Uncertainties (if applicable)
		abiraterone and for placebo + abiraterone) and from literature for enzalutamide (from the PREVAIL study).	abiraterone versus enzalutamide: Low In the comparison versus abiraterone: Low		
HRQoL	Mapped from EQ-5D-5L to EQ-5D-3L using Hernández Alava et al., 2017 algorithm.[49]	EQ-5D-5L sourced from the PROpel RCT (for olaparib with abiraterone and for placebo with abiraterone) were mapped to produce EQ-5D-3L utilities. Health state utilities were calculated using a MMRM analysis to determine mean HSU and SE for each health state in the model. The company fitted 4 models and chose the best fitting (model 2: HSU ~ progression status). In line with the findings of the model, the same HSU was applied across all arms of the model.	In the comparison of olaparib plus abiraterone versus enzalutamide: Low In the comparison versus abiraterone: High (pre-progression health state utility)	None	None

Abbreviations: AE – Adverse event; CTCAE – Common Terminology Criteria for Adverse Events; EAG – External Assessment Group; EQ-5D-3L – EuroQol Group 5-Dimension 3-Level Self-Report Questionnaire; EQ-5D-5L – EuroQol Group 5-Dimension 5-Level Self-Report Questionnaire; HR – Hazard ratio; HRQoL – Health-related quality of life; HSU – Health-state utility; ICER – Incremental cost-effectiveness ratio; MMRM – Mixed model for repeated measures; NICE – National Institute for Health and Care Excellence; NMA – Network meta-analysis; OS – Overall survival; PCWG-3 – Prostate Cancer Working Group 3; PFS – Progression-free survival; RCT – Randomised control trial; RECIST – Response Evaluation Criteria in Solid Tumours; rPFS – Radiographic progression-free survival : SE – Standard error; TA – Technology appraisal; TTD – Time to treatment discontinuation; TTDA – Time to treatment discontinuation with abiraterone.
Source: NICE TA951[46]

B.2.2 Resource use assumptions

In TA951, the following types of resource use and costs were applied in the model: drug acquisition, subsequent treatments, disease monitoring, management of adverse events (AEs), and end-of-life care.[46]

Drug acquisition costs for the intervention and comparators were based on their respective SmPCs given at their full licensed doses, and patients were assumed to receive 100% of their targeted dose. Treatment duration for olaparib with abiraterone was modelled independently using parametric distributions fitted to the time to discontinuation data from PROpel for each component of the regimen (TTD and TTDA), with TTD for enzalutamide assumed to be equal to abiraterone. The EAG deemed it inappropriate to use different functional forms to model PFS and TTD, as it implicitly de-couples treatment discontinuation from its primary cause (i.e., progression). The company accepted the EAG's preference for the generalised gamma extrapolation, which resulted in the time on the treatment curve remaining below PFS.

Subsequent treatments were associated with a one-off cost at the point of disease progression from each initial treatment. The proportion of patients who receive a subsequent treatment in the model was based on UK clinical expert opinion,[7] with an assumption that an additional proportion of patients would receive a further line of therapy based on data from PROpel. The duration of subsequent treatment was based on data from PROpel and a real-world survey of treatment patterns. The EAG agreed with the company's approach to modelling subsequent treatments, including the exclusion of subsequent re-treatment with NHAs from the modelled cost calculations (i.e., using NHS-appropriate subsequent therapy).

Disease monitoring healthcare utilisation rates were adopted from a previous NICE submission of enzalutamide (TA377) and assumed equivalent for olaparib with abiraterone and abiraterone.[44] A higher weekly frequency of healthcare resource utilisation (HCRU) was applied for the first three months, and then reduced from four months onwards, for olaparib, abiraterone, and enzalutamide. The EAG queried the

strictly 3-month application of treatment toxicity monitoring costs, so the company subsequently updated it to extend for the full model time horizon.

Management costs for AEs were based on treatment-related grade ≥3 events occurring in ≥5% of patients in each treatment arm of PROpel (olaparib with abiraterone and placebo plus abiraterone) and PREVAIL (enzalutamide), with costs applied as a one-off cost at the start of the model for all treatment arms. Skeletal-related AEs were applied as a one-time cost at disease progression, assuming an equivalent proportion of specific events between therapies in the model. End-of-life costs were applied as a one-off cost for patients upon death.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A clinical systematic literature review (SLR) was originally conducted on 9th September 2021 and periodically updated, with the latest update conducted on 4th June 2024, covering the period between November 2023 and June 2024. The aim of the SLR was to identify clinical trials evaluating treatments for patients with mCRPC who were asymptomatic or mildly symptomatic in the first-line setting. In total, the SLR identified 251 publications representing 75 unique studies. None of the studies were newly identified in the latest SLR update (June 2024).

Of the identified studies, only the TALAPRO-2 study investigated the use of talazoparib with enzalutamide in the population of interest. See **Appendix D** for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated in this appraisal.

B.3.2 List of relevant clinical effectiveness evidence

TALAPRO-2 is an ongoing, randomised, double-blind, Phase 3 trial and represents the primary source of clinical effectiveness evidence for talazoparib with enzalutamide for first-line treatment of patients with mCRPC for whom chemotherapy is not clinically indicated,[50,51] in line with its marketing authorisation.[14] A summary of the TALAPRO-2 trial is provided in **Table 4**.

Table 4: Clinical effectiveness evidence

Study	TALAPRO-2 (NCT03395197)
Study design	Randomised, double-blind, placebo-controlled, two-part, Phase 3 study
Population	Adult patients with mCRPC
Intervention(s)	Talazoparib (0.5 mg/day) in combination with enzalutamide (160 mg/day)
Comparator(s)	Placebo (0.5 mg/day) in combination with enzalutamide (160 mg/day)
Indicate if study supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	• rPFS (BICR-assessed) • OS • rPFS (investigator-assessed) • ORR • Safety • HRQoL
All other reported outcomes	• Duration of soft tissue response • Proportion of patients with PSA response of ≥50% • Time to PSA progression • Time to initiation of cytotoxic chemotherapy • Time to initiation of subsequent antineoplastic therapy • Time to first symptomatic skeletal event • Time to disease progression or death on the first subsequent antineoplastic therapy for prostate cancer (investigator-assessed) • Time to opiate use for prostate cancer pain • Pharmacokinetics
Key sources	Agarwal et al. 2023[51] TALAPRO-2 CSR[50]
Secondary sources	De Giorgi et al. 2024[52] Fizazi et al. 2024a[53] Fizazi et al. 2024b[54] Shore et al. 2024[55] Zschaebiz et al. 2024[56] Fay et al. 2023[57] Jones et al. 2023[58] Matsubara et al. 2023[59] Zschabitz et al. 2023[60]

Abbreviations: BICR – Blinded independent central review; HRQoL – Health-related quality of life; mCRPC – Metastatic castration-resistant prostate cancer; mg – milligram; OS – Overall survival; ORR – Objective response rate; PSA – Prostate-specific antigen; rPFS – Radiographic progression-free survival
Source: Agarwal et al. 2023[51] and TALAPRO-2 CSR[50]

B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Study design

TALAPRO-2 was designed as a randomised, double-blind, placebo-controlled, Phase 3 efficacy and safety study of talazoparib in combination with enzalutamide in patients with mCRPC.[50,51] The study consisted of two parts: Part 1 was open-label and non-randomised and evaluated safety, tolerability, and pharmacokinetics (PK); Part 2 was randomised, double-blind, and placebo-controlled, and evaluated efficacy and safety.[50] Enrolment began with Cohort 1, comprising the all-comers population (including all patients irrespective of homologous recombination repair [HRR] gene alterations).[50] Once enrolment was complete in Cohort 1, enrolment continued but was restricted to patients with HRR gene alterations (Cohort 2). Data presented in this submission are from the primary analysis of Part 2, Cohort 1, with a data cutoff date of 16th August 2022 and a median duration of follow-up for the primary outcome of 24.9 months for the talazoparib with enzalutamide group (talazoparib arm) and 24.6 months for the placebo with enzalutamide group (placebo arm). This cutoff date presents the final analysis for the primary outcome and interim analyses for the secondary outcomes.[50]

Eligible patients were adult men (age ≥18 years [≥20 years in Japan]) who were receiving ongoing ADT, had asymptomatic or mildly symptomatic mCRPC, had an Easter Cooperative Oncology Group (ECOG) performance status score of 0 or 1, had progressive disease at study entry, had adequate bone marrow function, and had not received previous life-prolonging systematic therapy for CRPC or mCRPC.[50,51] Patients were randomised 1:1 to receive either talazoparib or matching placebo (both at 0.5 mg/day) in combination with open-label enzalutamide (160 mg/day).[50]

The primary objective of the study was to demonstrate the superiority of talazoparib with enzalutamide to placebo with enzalutamide in prolonging blinded independent central review (BICR)-assessed rPFS, defined as time from randomisation to the first objective evidence of radiographic progression, or death due to any cause, whichever occurs first.[50,51] Secondary endpoints included OS, investigator-assessed

rPFS, objective response rate (ORR), duration of soft tissue response, and time to prostate-specific antigen (PSA) progression.[50] A full breakdown of the study characteristics of TALAPRO-2 is presented in **Table 5**.

Table 5: Study characteristics of TALAPRO-2

Study	TALAPRO 2: A Phase 3, randomised, double-blind, placebo-controlled study of talazoparib with enzalutamide in metastatic castration resistant prostate cancer
Study design and objective	Part 1 was open-label and non-randomised and evaluated the safety, tolerability, and PK of talazoparib in combination with enzalutamide. Part 2 was randomised, double-blind, placebo-controlled, and evaluated the efficacy and safety of talazoparib in combination with enzalutamide compared with placebo in combination with enzalutamide.
Study location(s)	Patients were treated across 287 sites in 26 countries in North America, Europe, Israel, South America, South Africa, and the Asia-Pacific region.
Method of randomisation	Patients were randomly assigned 1:1 by site personnel, using a centralised interactive web response system and a permuted block size of 4, to talazoparib with enzalutamide or matching placebo with enzalutamide. Randomisation was stratified by previous novel hormonal therapy or docetaxel for castration-sensitive prostate cancer (yes vs no) and HRR gene alteration status (deficient vs non-deficient or unknown). The sponsor, patients, and investigators were masked to talazoparib or placebo, while enzalutamide was open label.
Eligibility criteria for participants	**Key inclusion criteria:** • Histologically or cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features • Assessment of HRR mutation status by prospective analysis of blood, or tissue, or historical analysis, of most recent tumour tissue • Surgically or medically castrated, with serum testosterone ≤50 ng/dL at screening • Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan. • Progressive disease at study entry in the setting of medical or surgical castration • ECOG performance status ≤1 • Life expectancy ≥12 months as assessed by the investigator

	Key exclusion criteria: The following prior treatments were not permitted: • Any prior systematic cancer treatment initiated in the nmCRPC or mCRPC disease state. • Second-generation AR inhibitors, PARP inhibitors, cyclophosphamide, or mitoxantrone for prostate cancer • Platinum-based chemotherapy within 6 months prior to randomisation, or any history of disease progression on platinum-based therapy within 6 months • Prednisone >10 QD (or equivalents) The following prior treatments were permitted (under circumstances stated): • ADT and first-generation anti-androgens received in the CRPC disease state were permitted • Abiraterone in the castration-sensitive settings or hormonal therapy were not exclusionary if discontinued prior to randomisation. • Treatment with cytotoxic chemotherapy, biologic therapy, or radionuclide therapy received in the castration sensitive prostate cancer was not exclusionary if discontinued in the 28 days prior to randomisation. Other exclusion criteria • Major surgery within 2 weeks before randomisation, or palliative localised radiation therapy within 3 weeks before randomisation • Clinically significant cardiovascular disease, significant renal dysfunction, or significant hepatic dysfunction • Known or suspected brain metastasis or active leptomeningeal disease • Symptomatic or impending spinal cord compression or cauda equina syndrome • Any history of MDS, AML, or prior malignancy, except any of the following: carcinoma in situ or nonmelanoma skin cancer; prior malignancies ≥3 years before randomisation; Stage 0 or Stage 1 cancer <3 years before randomisation
Duration of study	Initiation date: 08/08/2017 Completion date: 16/08/2022

Trial drugs	Talazoparib (0.5 mg/day) in combination with enzalutamide (160 mg/day)
Primary outcome(s)	BICR-assessed rPFS, defined as the time from the date of randomisation to first objective evidence of radiographic progression as assessed in soft tissue per RECIST 1.1, or in bone per PCWG3 criteria, or death, whichever occurs first.
Key secondary outcomes	• Investigator-assessed rPFS • OS
Other outcomes of relevance to the NICE scope	• BICR-assessed ORR • Investigator-assessed ORR • Reporting of AEs and SAEs • Pain symptoms per BPI-SF – Question 3 • Cancer-specific global health status/QoL, functional scales, and symptom scales (EORTC-QLQ-C30) • Time to definitive deterioration – Global health status/QoL (QLC-C30) • Cancer-specific global health status/QoL, functioning, and symptoms outcome (EORTC-QLQ-PR25) • Time to definitive deterioration in participants reported disease specific urinary symptoms (EORTC-QLQ-PR25)
Other outcomes of interest	• BICR-assessed duration of response • Investigator-assessed duration of response • PSA response • Time to confirmed PSA progression: All-comers • Time to initiation of cytotoxic chemotherapy • Time to initiation of antineoplastic therapy • Time to first symptomatic skeletal event • Investigator-assessed PFS2 • Time to opiate use

Abbreviations: ADT – Androgen deprivation therapy; AE – Adverse event; AML – Acute myeloid leukaemia; AR – Androgen receptor; BICR – Blinded independent central review; BPI-SF – Brief Pain Inventory – Short Form; CRPC – Castration-resistant prostate cancer; CT – Computed tomography; dl – decilitre; ECOG – Easter Cooperative Oncology Group; EORTC QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire 30; EORTC QLQ-PR25 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate 25; HRR – Homologous recombination repair; mCRPC – Metastatic castration-resistant prostate cancer; MDS - Myelodysplastic syndrome; mg – milligram; MRI – Magnetic resonance imaging; ng – nanogram; nmCRPC – Non-metastatic castration-resistant prostate cancer; ORR – Objective response rate; OS – Overall survival; PARP – Poly ADP-ribose polymerase; PFS2 – Progression-free survival on next line therapy; PK – Pharmacokinetics; PSA – Prostate-specific antigen; QD – Once daily; QoL – Quality of life; RECIST - Response Evaluation Criteria in Solid Tumours; rPFS – Radiographic progression-free survival; SAE – Serious adverse event
Source: Agarwal et al. 2023[51] and TALAPRO-2 CSR[50]

B.3.3.2 Baseline characteristics of trial participants

Demographic and baseline characteristics of randomised patients are presented in **Table 6**. In total, 805 patients were enrolled and randomly assigned to the

talazoparib with enzalutamide arm (N=402) or placebo with enzalutamide arm (N=403), representing the intention-to-treat (ITT) population.[50,51]

Patient characteristics were consistent across the two arms.[50,51] Both arms had the same median age of 71 years.[50] A similar proportion of patients in each arm had received prior treatment with hormone therapy (abiraterone [5% and 6%] and orteronel [<1%]).[50] The rate of prior taxane-based chemotherapy was also aligned across the treatment arms (21% and 23%).[50]

Given it was a randomisation stratification factor, the HRR gene alteration status was the same across both treatment arms, with 21% of participants being HRR-deficient and 79% being HRR-non-deficient or of an unknown status.[51] The rate of BRCA alterations was similar in both arms (7% in the talazoparib arm and 8% in the placebo arm.[51]

Table 6: Baseline patient demographics and disease characteristics in TALAPRO-2 (N=805)

Characteristic	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Total (n=805)
Median age, years (range)	71 (66-76)	71 (65-76)	-
Race, n (%)			
White	243 (60)	255 (63)	498 (62)
Black or African American	11 (3)	5 (1)	16 (2)
Asian	127 (32)	120 (30)	247 (31)
Multiracial	0	1 (<1)	1 (<1)
Other[a]	2 (<1)	1 (<1)	3 (<1)
Not reported	19 (5)	21 (5)	40 (5)
Renal impairment, n (%) [b,c]			
None or mild	344 (86)	347 (86)	691 (86)
Moderate	42 (10)	41 (10)	83 (10)
Median baseline serum PSA, µg/L (range)	18.2 (6.9-59.4)	16.2 (6.4-53.4)	-
Median baseline circulating tumour cell count, cells per 7.5 mL of blood	1 (0-7)	1 (0-6)	-

Characteristic	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Total (n=805)
Gleason score, n (%) [b]			
<8	117 (29)	113 (28)	230 (29)
≥8	281 (70)	283 (70)	564 (70)
Disease site, n (%)			
Bone (including with soft tissue component)	349 (87)	342 (85)	691 (86)
Lymph node	147 (37)	167 (41)	314 (39)
Visceral (lung)	45 (11)	61 (15)	106 (13)
Visceral (liver)	12 (3)	16 (4)	28 (3)
Other soft tissue	37 (9)	33 (8)	70 (9)
ECOG performance status, n (%)			
0	259 (64)	271 (67)	530 (66)
1	143 (36)	132 (33)	275 (34)
Previous taxane-based chemotherapy, n (%)[d]	86 (21)	93 (23)	179 (22)
Previous treatment with novel hormonal therapy, n (%)	23 (6)	27 (7)	50 (6)
Abiraterone	21 (5)	25 (6)	46 (6)
Orteronel	2 (<1)	2 (<1)	4 (<1)
HRR gene alteration status by randomisation stratification, n (%)			
Deficient	85 (21)	84 (21)	169 (21)
Non-deficient or unknown	317 (79)	319 (79)	636 (79)
HRR gene alteration status by prospective tumour tissue testing, n (%)[e]			
Deficient	85 (21)	82 (20)	167 (21)
Non-deficient	207 (51)	219 (54)	426 (53)
Unknown	110 (27)	102 (25)	212 (26)
BRCA1/2 alteration	27 (7)	32 (8)	59 (7)

[a] American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander.

[b] Not reported for the remaining patients.

[c] Moderate renal impairment defined as 30–59 mL/min per 1.73 m².

[d] All received docetaxel.

[e] Exploratory endpoint analysis by prospective tumour tissue testing to separate unknown from non-deficient HRR gene alteration status. Prospective "unknown" status for HRR gene alteration status primarily reflects the sample(s) submitted to Foundation Medicine not being analysed (typically due to failed quality control metrics) or test results not being reported (due to limitations in sample quality or purity).

Abbreviations: BRCA – Breast cancer gene; ECOG – Easter Cooperative Oncology Group; g – gram; HRR – Homologous recombination repair; L – litre; ml – millilitre; PSA – Prostate-specific antigen

Source: Agarwal et al. 2023 – Table 1[51]

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 Study population and patient disposition

Patient data sets analysed in the TALAPRO-2 study are described in **Table 7**. This submission is focused on results from Cohort 1 Part 2, with clinical efficacy analyses performed on the ITT population and safety analyses performed on the safety population.

Table 7: TALAPRO-2 analysis sets (Part 2: Double-blind, placebo-controlled, randomised)

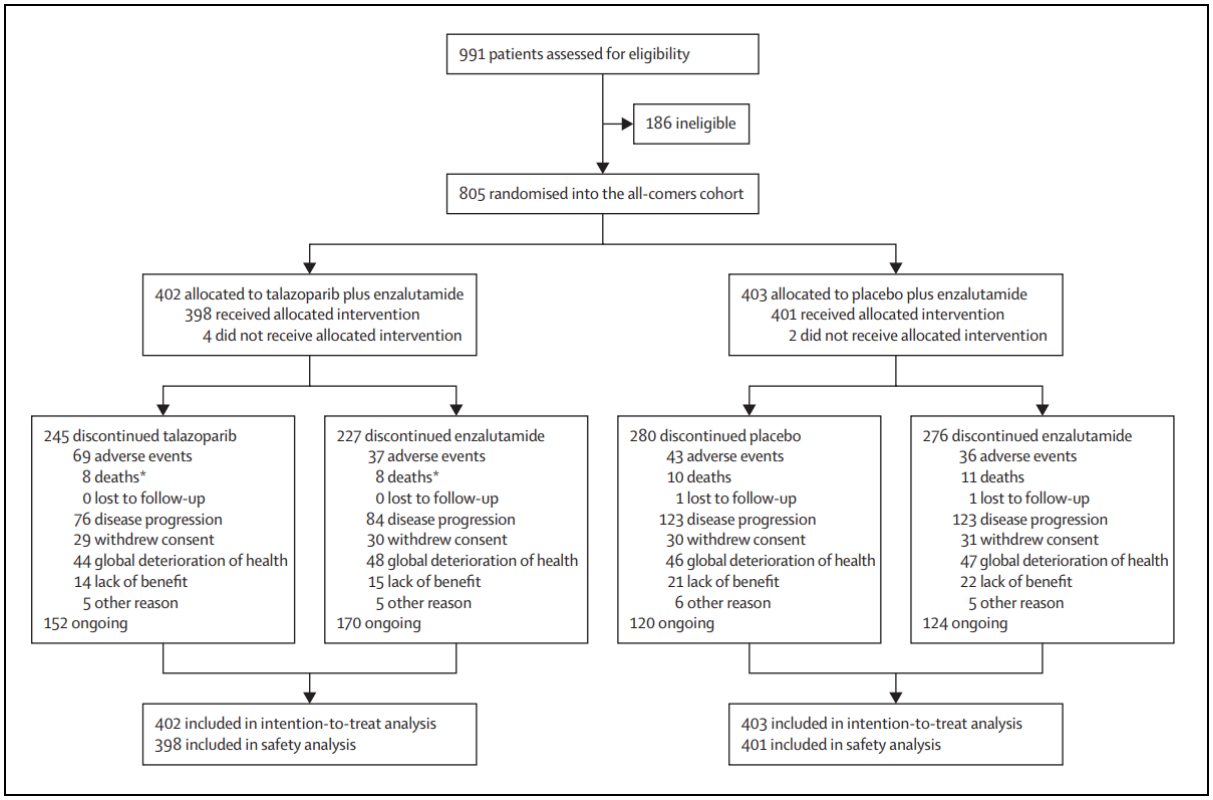
Analysis set	Description	Applicable analysis
All-comers population	Participants unselected for HRR status enrolled in Cohort 1.	--
Intent-to-treat	All participants randomly assigned to double-blind study treatment in Part 2 whether or not treatment was administered.	Efficacy analyses Select baseline characteristics summaries
Safety population	All participants who received at least 1 dose of study treatment (talazoparib, placebo, or enzalutamide).	Safety analyses Select baseline characteristics summaries
PK population	All participants who received at least 1 dose of study treatment and provided an evaluable PK sample.	PK analyses
CTC evaluable population	All participants from the Safety Analysis set with a baseline CTC assessment and at least 1 post-baseline CTC assessment.	CTC analyses
PRO population	All participants from the ITT population who completed a baseline PRO assessment and had at least 1 post-baseline PRO assessment prior to the end of study.	PRO analyses

Abbreviations: CTC – Circulating tumour cells; HRR – Homologous recombination repair; ITT – Intention-to-treat; PK – Pharmacokinetics; PRO – Patient-reported outcomes
Source: TALAPRO-2 CSR – Table 5[50]

Figure 2 displays the patient disposition in TALAPRO-2. Of the 991 participants enrolled, 805 participants were randomised to treatment with either talazoparib with enzalutamide or placebo with enzalutamide; the remaining 186 participants were screen failures.[50,51] Discontinuation during the treatment phase was reported for 61.6% (245/398) and 69.8% (280/401) of participants in the talazoparib and placebo

arms, respectively, with progressive disease (PD) being the most frequently reported reason for discontinuation.[50,51] The final number of participants included in the ITT analysis was 402 for the talazoparib arm and 403 for the placebo arm.[50,51]

Figure 2: TALAPRO-2: patient disposition



Two patients (one in each treatment arm) who received enzalutamide but not talazoparib/placebo were excluded from the list of patients who discontinued treatment. One patient withdrew from the study with no protocol deviation reported; the second patient had a protocol deviation reported and discontinued from the study due to no longer meeting eligibility criteria.
*Discontinuation due to death was reported for one patient in error. The patient discontinued both talazoparib and enzalutamide due to the same adverse event on the same date.
Source: Agarwal et al. 2023 – Figure 1[51]

B.3.4.2 Statistical analyses

Details of the statistical methods used in TALAPRO-2 are presented in **Table 8**.

Table 8: TALAPRO-2: Statistical methods

Hypothesis objective	Primary objective: • To demonstrate the superiority of talazoparib with enzalutamide versus placebo with enzalutamide in prolonging BICR-assessed rPFS Key secondary objectives: • To demonstrate the superiority of talazoparib with enzalutamide to placebo with enzalutamide in prolonging OS • To evaluate safety/toxicity profile of talazoparib and enzalutamide when administer in combination
Sample size, power calculation	Sample size and power calculations were based on a stratified log-rank test. For the primary comparison in the all-comers population, 333 rPFS events would provide 85% power to detect a HR of 0.696 using a one-sided stratified log-rank test at a significance level of 0.0125 based on a two-look group sequential design. OS was tested only if the rPFS results showed statistically significant improvement in a hierarchical stepwise procedure to preserve the overall type I error. For OS in the all-comers population, 438 OS events would provide 77% power to detect an HR of 0.75 using a one-sided stratified log-rank test at a significance level of 0.0125 based on a three-look group sequential design with O'Brien-Fleming α-spending function.
Statistical analysis	Time-to-event endpoints were compared between treatment arms using a stratified log-rank test. HRs and associated two-sided 95% CIs were estimated by a Cox proportional hazards model. Median time-to-event endpoints were estimated by the Kaplan-Meier method, and 95% CIs were based on the Brookmeyer-Crowley method. For the subgroup analysis of rPFS (except for the BRCA status), the HR was based on an unstratified Cox model with treatment as the only covariate due to the small number of patients in some of the subgroups. Missing data was not imputed, except for date of birth (if year of birth is available), date of last dose of study treatment, death date, date of start of follow-up cancer therapy, and adverse events. SAS version 9.4 statistical software was used.
Interim analyses	A prespecified interim futility analysis of rPFS was planned using the O'Brien-Fleming β-spending function when approximately 50% of the expected events (167 rPFS events) had occurred. The interim rPFS results were assessed by an external data monitoring committee, and the all-comers cohort would be stopped for futility if the boundary was crossed at the interim analysis. There were two interim analyses of OS in the all-comers population: the first at the time of the final analysis of rPFS and the second when approximately 75% of the total required events (327 OS events) had occurred. Other endpoints had no adjustment for multiplicity.

Abbreviations: BICR – Blinded independent central review; BRCA – Breast cancer gene; CI – Confidence interval; HR – Hazard ratio; OS – Overall survival; rPFS – Radiographic progression-free survival; SAS – Statistical analysis system

Source: Agarwal et al. 2023[51] and TALAPRO-2 CSR[50]

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A quality assessment of TALAPRO-2 was performed using the NICE Single Technology Appraisal Evidence Submission Checklist for assessment of risk of bias in randomised control trials (RCTs) and is presented in **Table 9**. The quality assessment of other studies included in the clinical SLR is presented in **Appendix D**.

Table 9: TALAPRO-2: quality assessment

Questions	TALAPRO-2
Was randomisation carried out appropriately?	Yes – randomisation was carried out as per the pre-specified randomisation method; patients were randomly assigned 1:1 by site personnel, using a centralised interactive web response system and a permuted block size of 4, to the talazoparib group or the matching placebo group. Randomisation was stratified by previous novel hormonal therapy or docetaxel for castration-sensitive prostate cancer (yes vs no) and HRR gene alteration status (deficient vs non-deficient or unknown).
Was the concealment of treatment allocation adequate?	Yes – randomisation data was kept strictly confidential.
Were the arms similar at the outset of the study in terms of prognostic factors?	Yes – demographic and baseline characteristics were well balanced between the two treatment arms.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes – the sponsor, patients, and investigators were blinded to treatment allocations. Enzalutamide was open-label.
Were there any unexpected imbalances in dropouts between arms?	No – there were no unexpected imbalances in dropouts between arms. Withdrawals by patient were similar in both arms (29 in the talazoparib arm and 30 in the placebo arm).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No – there is no evidence to suggest that the authors measured more outcomes than they reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes – the ITT population (all-comers/all randomised participants) was used for analysis of the primary endpoint and other secondary efficacy endpoints.

Abbreviations: HRR – Homologous recombination repair; ITT – Intention-to-treat

Source: Agarwal et al. 2023[51] and TALAPRO-2 CSR[50]

B.3.6 Clinical effectiveness results of the relevant studies

The focus of this submission is Part 2, Cohort 1 of TALAPRO-2, with data presented from data cutoff on 16th August 2022 (the primary analysis of Part 2, Cohort 1). The median follow-up for the primary analysis at the time of this data cutoff was 24.9 months for the talazoparib arm and 24.6 months for the placebo arm.

B.3.6.1 Primary efficacy endpoint: rPFS by BICR

The BICR-assessed rPFS results for the Cohort 1 Part 2 ITT population (i.e., all-comers) are presented in

Table 10 and **Figure 3**. Based on the pre-planned, final data cut-off date of August 16th 2022 (median follow-up for the primary analysis: 24.9 months for the talazoparib arm, 24.6 months for the placebo arm), the observed hazard ratio (HR) for BICR-assessed rPFS was 0.63 (95% CI 0.51, 0.78; p<0.0001), highlighting a statistically significant improvement with talazoparib with enzalutamide compared to placebo with enzalutamide.[50] The trial therefore met its primary endpoint. Median BICR-assessed rPFS was NR (95% CI 27.5 months, NR) in the talazoparib arm and 21.9 months (16.6, 25.1) in the placebo arm.[50]

Table 10: TALAPRO-2: Summary of BICR-assessed rPFS for the Cohort 1 Part 2 all-comers ITT population (N=805)

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median rPFS by BICR, months (95% CI)[a]	NR (27.5, NR)	21.9 (16.6, 25.1)	0.627 (0.506, 0.777)	<0.0001
Events (%)	151 (37.6)	191 (47.4)	--	--
Probability of being event-free[b] (95% CI)				
6 months	[redacted]	[redacted]	--	--
12 months	[redacted]	[redacted]	--	--
24 months	[redacted]	[redacted]	--	--
36 months	[redacted]	[redacted]	--	--

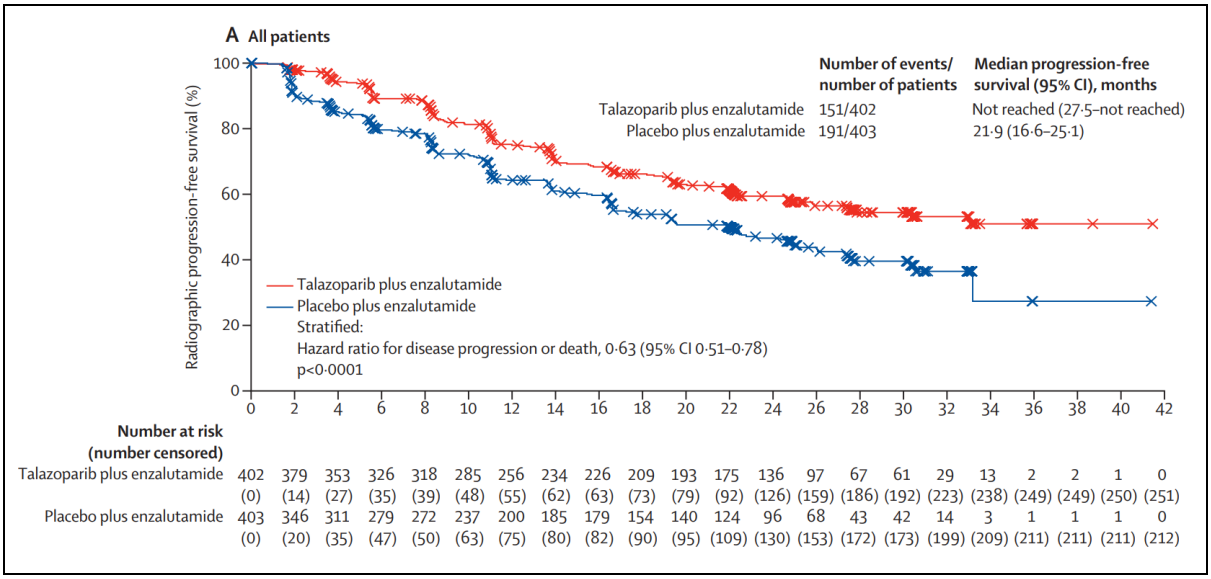
[a] Based on the Brookmeyer-Crowley method.

[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.

Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; ITT – Intention-to-treat; NR – Not reached; rPFS – Radiographic progression-free survival

Source: Agarwal et al. 2023[51] and TALAPRO-2 CSR – Table 20[50]

Figure 3: Kaplan-Meier plot of BICR-assessed rPFS for the Cohort 1 Part 2 all-comers ITT population (N=805)



Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; HRR – Homologous recombination repair; ITT – Intention-to-treat; rPFS – Radiographic progression-free survival

Source: Agarwal et al. 2023 – Figure 2[51]

B.3.6.2 Key secondary efficacy endpoint: Investigator-assessed rPFS

A key secondary outcome of TALAPRO-2 was rPFS by investigator assessment, with results shown in **Table 11** and **Figure 4**. The observed stratified HR for

talazoparib with enzalutamide versus placebo with enzalutamide was [redacted], highlighting [redacted].[50] Median (95% CI) rPFS based on Kaplan-Meier estimates was [redacted] months for participants in the talazoparib arm and [redacted] months for participants in the placebo arm.[50]

Table 11: TALAPRO-2: Summary of investigator-assessed rPFS for the Cohort 1 Part 2 all-comers ITT population (N=805)

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median[a] (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
Number of events (%)	[redacted]	[redacted]	-	-
Probability of being event-free[b] (95% CI)				
6 months	[redacted]	[redacted]	-	-
12 months	[redacted]	[redacted]	-	-
24 months	[redacted]	[redacted]	-	-
36 months	[redacted]	[redacted]	-	-

[a] Based on the Brookmeyer-Crowley method.

[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; NR – Not reached; rPFS – Radiographic progression-free survival

Source: TALAPRO-2 CSR – Table 21[50]

Figure 4: TALAPRO-2: Kaplan-Meier plot of investigator-assessed rPFS for the Cohort 1 Part 2 all-comers ITT population (N=805)

Abbreviations: CI – Confidence interval; HR – Hazard ratio; ITT – Intention-to-treat; rPFS – Radiographic progression-free survival

Source: TALAPRO-2 CSR - Figure 4[50]

B.3.6.3 Key secondary efficacy endpoint: OS

The OS results for the Cohort 1 Part 2 all-comers ITT population are presented in **Table 12** and **Figure 5**. The OS data are immature; only 30.6% of patients in the talazoparib arm and 32.0% of patients in the placebo arm had died at data cutoff (median follow-up: [redacted] months for the talazoparib arm and [redacted] months for the placebo arm).[50] The HR for death was 0.888 (95% CI 0.693, 1.138; 2-sided p=0.35).[50] The probability of being event-free was numerically in favour of the talazoparib arm, recorded at [redacted] and [redacted] at 12 months, [redacted] and [redacted] at 24 months, and [redacted] and [redacted] at 36 months for the talazoparib and placebo arms, respectively.[50]

Table 12: Summary of OS for the Cohort 1 Part 2 all-comers ITT population (N=805)

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median[a] (95% CI), months	[redacted]	[redacted]	0.888 (0.693, 1.138)	0.3472
Number of events (%)	30.6	32.0	-	-
Probability of being event-free[b] (95% CI)				
6 months	[redacted]	[redacted]	-	-
12 months	[redacted]	[redacted]	-	-
24 months	[redacted]	[redacted]	-	-
36 months	[redacted]	[redacted]	-	-

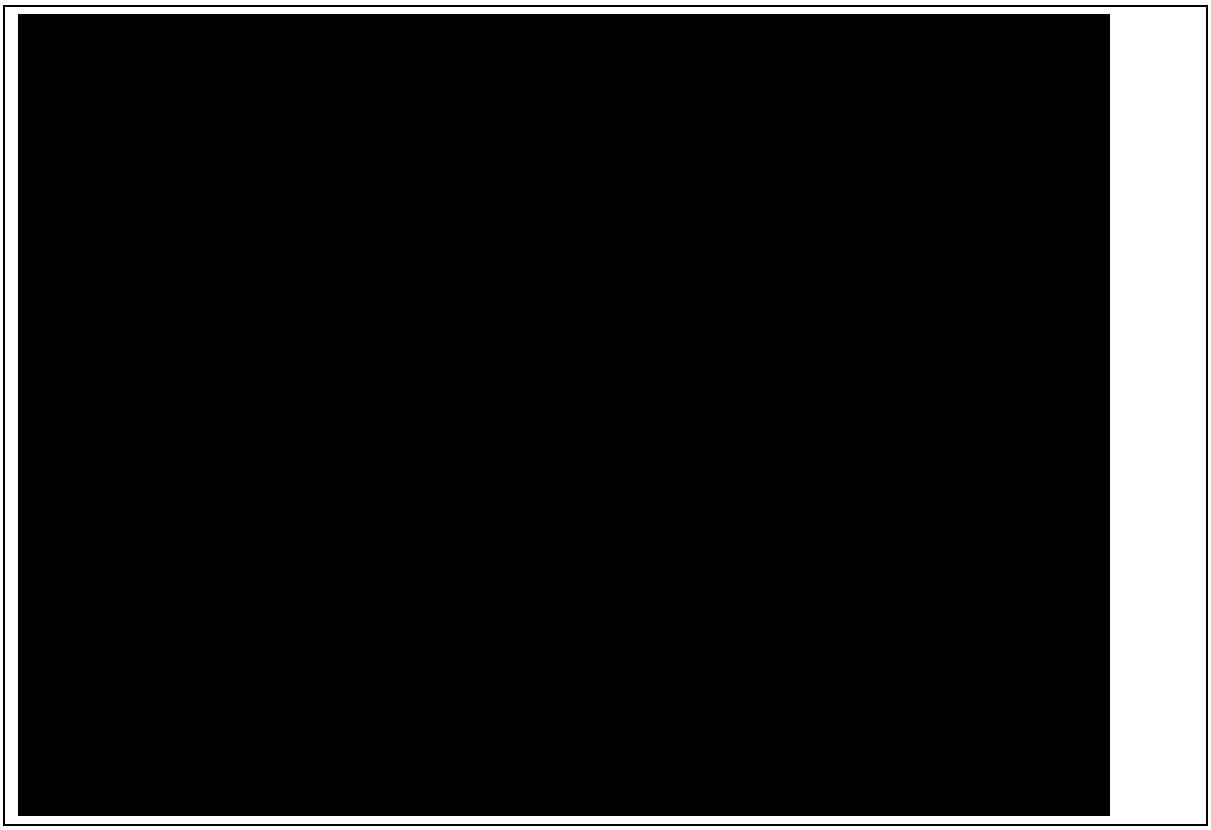
[a] Based on the Brookmeyer-Crowley method.

[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; NR – Not reached; OS – Overall survival

Source: Agarwal et al. 2023[51] and TALAPRO-2 CSR – Table 23[50]

Figure 5: Kaplan-Meier plot of OS for the Cohort 1 Part 2 all-comers ITT population (N=805)



Abbreviations: CI – Confidence interval; HR – Hazard ratio; ITT – Intention-to-treat; OS – Overall survival

Source: TALAPRO-2 CSR – Figure 6[50]

B.3.6.4 Other secondary efficacy endpoints

A summary of the results of other secondary efficacy endpoints in the Cohort 1 Part 2 all-comers ITT population is presented in **Table 13.** Confirmed ORR in patients with measurable disease at baseline was 62% (95% CI 52.4, 70.4) for the talazoparib arm and 44% (95% CI 35.3, 52.8) for the placebo arm, with a complete response in 37.5% and 18.2% of patients, respectively.[50,51]

The PSA response rate was 83.6% (95% CI 79.6, 87.1) in the talazoparib arm and 72.1% (95% CI 67.4, 76.5) in the placebo arm.[50,51] The difference in PSA response was statistically significant at 11.5% (95% CI 5.8, 17.2; two-sided p-value=0.0001).[50]

The observed stratified HR (talazoparib arm vs placebo arm) for time to PSA progression was 0.715 (95% CI 0.577, 0.886; two-sided p-value=0.0020) indicating statistical significance in favour of the talazoparib arm.[50,51] Median time to PSA progression was 26.7 months (95% CI 21.2, 30.4) for the talazoparib arm and 17.5 months (95% CI 14.1, 20.8) for the placebo arm.[50]

Table 13: Summary of secondary efficacy endpoints for the Cohort 1 Part 2 all-comers ITT population (N=805)

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Best overall response[a], n (%)				
Complete response	45 (38)	24 (18)	-	-
Partial response	29 (24)	34 (26)	-	-
Stable disease	36 (30)	38 (29)	-	-
Progressive disease	7 (6)	30 (23)	-	-
Not evaluable	3 (2)	6 (5)	-	-
Objective response[a], n (%; 95% CI)	74 (62; 52.4, 70.4)	58 (44; 35.3, 52.8)	-	0.0050
Median duration of response[b] (95% CI), months	20.4 (16.1, NR)	19.8 (12.9, NR)	-	-
PSA response ≥50%[c], n (%; 95% CI)	331 (84; 79.6-97.1)	284 (72; 67.4-76.5)	-	0.0001
Time to PSA progression				
Patients with progression, n (%)	164 (41)	177 (44)	-	-
Median time to progression (95% CI), months	26.7 (21.2, 30.4)	17.5 (14.1, 20.8)	0.72 (0.58, 0.89)	0.0020
Time to initiation of cytotoxic chemotherapy				
Patients with use, n (%)	83 (21)	139 (34)	-	-

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median time to use (95% CI), months	NR (37.0, NR)	NR (32.3, NR)	0.49 (0.38, 0.65)	<0.0001
Time to first initiation of subsequent antineoplastic therapy				
Patients with use, n (%)	114 (28)	176 (44)	-	-
Median time to use (95% CI), months	NR (37.0, NR)	28.3 (23.5, NR)	0.54 (0.42, 0.68)	<0.0001
Time to first symptomatic skeletal event				
Patients with event, n (%)	91 (23)	93 (23)	-	-
Median time to first event (95% CI), months	NR (NR)	NR (NR)	0.88 (0.66, 1.18)	0.41
PFS2[d]				
Patients with event, n (%)	126 (31)	143 (35)	-	-
Median PFS2 (95% CI), months	36.4 (33.5, NR)	35.3 (28.6, NR)	0.77 (0.61, 0.98)	0.036

[a] Only includes patients with measurable soft tissue disease at baseline per BICR: talazoparib arm (n=120); placebo arm (n=132).

[b] Only includes patients with confirmed complete response or partial response: talazoparib arm (n=74); placebo arm (n=58).

[c] Only includes patients with a baseline PSA value and at least one post-baseline PSA value: talazoparib arm (n=396); placebo arm (n=394).

[d] PFS2 based on investigator assessment (time from randomisation to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurs first).

Abbreviations: CI – Confidence interval; NR – Not reached; PFS2 – Progression-free survival on next line therapy; PSA – Prostate-specific antigen

Source: Agarwal et al 2023 - Table 2[51]

B.3.6.5 Patient-reported outcomes

Part 2 of the TALAPRO-2 study included a number of pre-specified PROs as secondary endpoints. Pain symptoms were measured using Brief Pain Inventory – Short Form (BPI-SF).[50] Cancer-specific global health status (GHS), quality of life (QoL), functioning, and symptoms outcomes were measured using European Organisation for Research and Treatment Quality of Life Cancer Questionnaire 30 (EORTC-QLQ-C30) and the prostate cancer-specific questionnaire, EORTC-QLQ-PR25. Overall QoL was measured using EuroQol-5 dimensions-5 levels (EQ-5D-5L).[50]

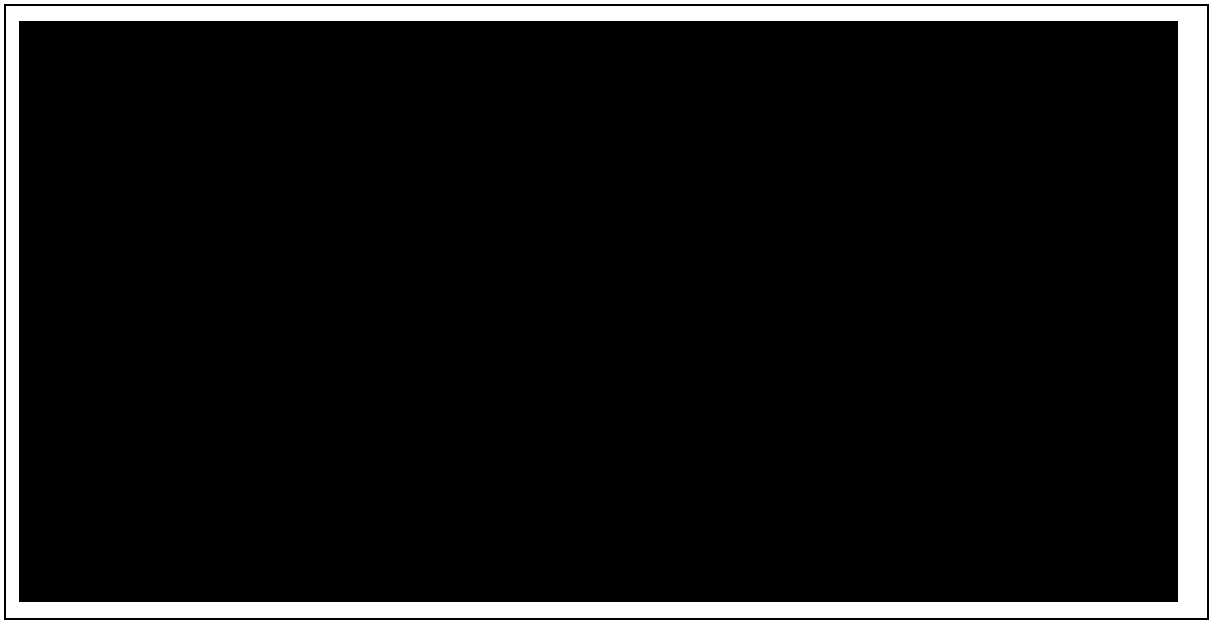
In terms of pain symptoms, as measured by BPI-SF question 3, there [redacted] in the estimated mean value of worst pain in the last 24 hours between the talazoparib and placebo arms.[50] The stratified HR for talazoparib with enzalutamide versus placebo with enzalutamide for TTD in Participant Reported

Pain Symptoms was [redacted].[50] The median time-to-definitive deterioration (TTDD) was [redacted] for participants in both treatment arms.[50]

Overall cancer-related QoL, as measured by EORTC-QLQ-C30, was [redacted] across all functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) [redacted].[50] Differences between treatment arms [redacted] for GHS/QOL, [redacted] (as measured by a 10-point difference).[50] In terms of the EORTC-QLQ-C30 symptom scales, there [redacted] for GHS/QoL, fatigue, nausea/vomiting, dyspnoea, and appetite loss, [redacted] (as measured by a 10-point difference).[50] Median TTDD in GHS/QoL was [redacted] for the talazoparib arm than the placebo arm ([redacted] months vs [redacted] months; HR: [redacted]).[50]

Overall QoL, as measured by EQ-5D-5L, [redacted], as shown in **Figure 6**.

Figure 6: Plot of EQ-5D-5L index scores change from baseline in the Cohort 1 Part 2 PRO population



N1: Number of participants in the talazoparib with enzalutamide arm at each assessment time point.
N2: Number of participants in the placebo with enzalutamide arm at each assessment time point.
EQ-5D-5L index scores are utility scores calculated by applying tariffs for UK to responses on the EQ-5D-5L.
Abbreviations: EQ-5D-5L – EuroQol-5 Dimensions-5 Levels; LTFU – Long term follow up; W – Week

In terms of prostate cancer-specific QoL, as measured by EORTC-QLQ-PR25, there was [redacted] across all functional and symptom scales, with [redacted] between the treatment arms.[50]

B.3.7 Subgroup analysis

According to NICE guidance for proportionate cost comparison appriasals,[2,3] subgroup analyses should only be provided *"if the technology does not provide similar or greater health benefits at a similar or lower cost to the comparator in the full population for whom the comparator has been recommended by NICE".* Given that the NMA (see **Section B.3.9.3)** robustly demonstrates that talazoparib with enzalutamide has similar efficacy to olaparib with abiraterone in the full population, subgroup analyses are not needed for this evidence submission under the proportionate approach.

Nevertheless, the TALAPRO-2 study confirmed that talazoparib with enzalutamide has a consistent treatment effect across key subgroups. The following pre-specified subgroup analyses were performed for the primary endpoint (BICR-assessed rPFS)[50]:

- Age (<70 years vs ≥70 years)
- Geographical region (Asia; European Union [EU] and UK; North America; or rest of the world)
- ECOG performance status (0 vs 1)
- Gleason score (<8 vs ≥8)
- Stage (M0 vs M1)
- Type of progression (PSA only vs imaging-based with or without PSA progression)
- Baseline PSA (<median vs ≥median)
- Site of metastasis (bone only vs soft tissue only vs bone and soft tissue)
- Previous taxane or novel hormonal therapy for castration sensitive prostate cancer (yes vs no)
- HRR gene alteration status (classed as deficient vs nondeficient or unknown by randomisation stratification)

Post-hoc subgroup analyses of BICR-assessed rPFS were also performed by BRCA1/2 status, HHR gene alteration status, and prospective tumour tissue testing.[50]

Across all prespecified subgroups (including across HRR subgroups: BRCA and ATM), the BICR-assessed rPFS benefit of talazoparib with enzalutamide [redacted]. In the primary analysis, the HR was 0.627 (95 CI 0.506, 0.777; p<0.0001), while in the pre-specified subgroup analyses the HR ranged from [redacted].

Given the significant treatment effect in the all-comers population and consistency across subgroups, the all-comers population is the focus of this submission.

B.3.8 Meta-analysis

As the SLR identified only one relevant trial evaluating talazoparib with enzalutamide in the population of interest for this NICE scope (TALAPRO-2), a meta-analysis is not required.

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Identification of relevant studies

A network meta-analysis (NMA) was conducted to estimate the comparative efficacy of first-line treatments, including talazoparib with enzalutamide, for patients with mCRPC who were asymptomatic or mildly symptomatic. The NMA was originally conducted in March 2023 based on an SLR from 3 October 2022 (hereafter referred to as the original NMA).[61] For the purposes of this NICE appraisal, the NMA was updated in July 2024, based on the latest SLR update from 4 June 2024 (hereafter referred to as the NMA update).

A feasibility assessment was undertaken to determine the suitability of an NMA to indirectly compare talazoparib with enzalutamide and olaparib with abiraterone and to determine the presence of heterogeneity in terms of trial design characteristics, patient eligibility criteria, baseline patient characteristics, outcome characteristics (i.e., definitions and methods of reporting outcomes).[62] In the original NMA, the

feasibility assessment had a broader scope than the scope of this appraisal as the outputs were being used for reimbursement submissions globally. The original NMA feasibility assessment confirmed that there were no significant imbalances in prognostic factors or treatment effect modifiers (TEMs) across the studies in the network, meaning that an NMA was feasible. NMAs were deemed feasible for the following outcomes: OS, rPFS, ORR, PSA response, and time to PSA progression. Of the 48 studies included in the October 2022 SLR, 38 were included in the original NMA for at least one outcome of interest (**Appendix J**); nine did not have available data and one was considered insufficiently similar based on the qualitative assessment of heterogeneity. The network diagrams for each outcome of the original NMA are provided in **Appendix J**.

The scope of the original NMA was adapted for the NMA update to focus on the decision problem addressed in this NICE appraisal: to estimate the comparative efficacy of talazoparib plus enzalutamide versus olaparib with abiraterone and determine whether an assumption of similar efficacy is appropriate (**Section B.1.1**). Studies not required to form a connection between talazoparib with enzalutamide and olaparib with abiraterone were excluded from the NMA update (n=30), resulting in a “restricted network” relative to the original NMA.

Twenty-seven newly identified studies from the SLR update (June 2024) were assessed for inclusion in the NMA update along with the nine studies previously without available data. None were considered relevant to the decision problem addressed in this NICE appraisal, predominantly due to a lack of relevance of included comparators (**Table 14**).

Table 14: List of newly identified studies excluded from NMA update (N=36)

Trial Identifier	Interventions
Studies without published data at the time of original NMA (n=9)	
CASPAR (NCT04455750)	Placebo + Enzalutamide vs Rucaparib + Enzalutamide
KEYNOTE-641 (NCT03834493)	Pembrolizumab + Enzalutamide vs Placebo + Enzalutamide
NCT04056754	Placebo + Prednisone vs Abiraterone + Prednisone
ESCALATE (NCT04237584)	Placebo + Enzalutamide + Darolutamide vs Radium-223 + Enzalutamide + Darolutamide

Trial Identifier	Interventions
GUIDE (NCT04918810)	Docetaxel vs Docetaxel
NCT03356444	Docetaxel vs Abiraterone
CHAARTED2 (NCT03419234)	Abiraterone + Prednisone vs Cabazitaxel + Abiraterone + Prednisone
GERICO10 (NCT01254513)	Docetaxel + Prednisone vs Docetaxel + Prednisone
ARACOG (NCT04335682)	Enzalutamide vs Darolutamide
Studies newly identified since the original NMA (n=27)	
STAMPEDE (NCT00268476)	Standard of care (Androgen Deprivation Therapy [ie., Docetaxel 75 mg + Prednisolone]) vs Abiraterone + Androgen Deprivation Therapy (Docetaxel 75 mg + Abiraterone Acetate and Prednisolone)
VENICE (NCT00519285)	Aflibercept vs Placebo
NR (Taplin 2019, updated 2023)	Galeterone vs Enzalutamide
PRESIDE (NCT02288247)	Part 2: Enzalutamide + Docetaxel + Prednisolone/Prednisone vs Placebo + Docetaxel + Prednisolone/Prednisone
NCT01867333	Enzalutamide
NR (Manikandan 2005, updated 2023)	Diethylstilboestrol + Aspirin vs Bicalutamide
ARTO (NCT03449719)	Abiraterone + Stereotactic body radiation therapy
VIABLE NCT02111577	Vaccine + Docetaxel + Prednisolone/Prednisone vs Placebo + Docetaxel + Prednisolone/Prednisone
SAKK 08/11 NCT01707966	Orteronel + Best Supportive Care vs Placebo
NCT00090363	Zibotentan vs Zibotentan vs Placebo
NCT03344211	Enzalutamide vs Enzalutamide + Radium-223
SAKK 08/14 NCT02640534	Enzalutamide + Metformin vs Enzalutamide
NR (Carducci 2007, updated 2023)	Atrasentan vs Placebo
NR (Azad 2014, updated 2023)	Vandetanib + Bicalutamide vs Bicalutamide
NR (Arlen 2006, updated 2023)	Vaccine vs Vaccine + Docetaxel
NR (Eymard 2007, updated 2023)	Docetaxel + Estramustine vs Docetaxel
NCT01685125	Abiraterone + Prednisolone/Prednisone vs Abiraterone + Prednisolone/Prednisone + Dasatinib
NR (Heidenreich 2013, updated 2023)	Docetaxel + Prednisolone/Prednisone + Intetumumab vs Docetaxel + Prednisolone/Prednisone + Placebo
NCT01234311	Tasquinimod vs Placebo
ENTHUSE NCT00554229	Zibotentan + Standard of care vs Placebo
ELM-PC 4 NCT01193244	Orteronel + Prednisolone/Prednisone vs Placebo + Prednisolone/Prednisone
NCT00560482	Placebo vs Tasquinimod

Trial Identifier	Interventions
CA184-095 NCT01057810	Placebo vs Ipilimumab
ProCAID NCT02121639	Capivasertib + Docetaxel + Prednisolone/Prednisone vs Placebo + Docetaxel + Prednisolone/Prednisone
ENZA-p ANZUP-1901 NCT04419402	Enzalutamide + 177Lu-PSMA-617 vs Enzalutamide
ProBio NCT03903835	Standard of care vs Androgen Receptor Pathway Inhibitor vs Taxanes
REASURE ISRCTN17805587	Radium-223

Abbreviations: Lu – Lutetium; mg – milligram; NR – Not reported;; PSMA – Prostate-specific membrane antigen

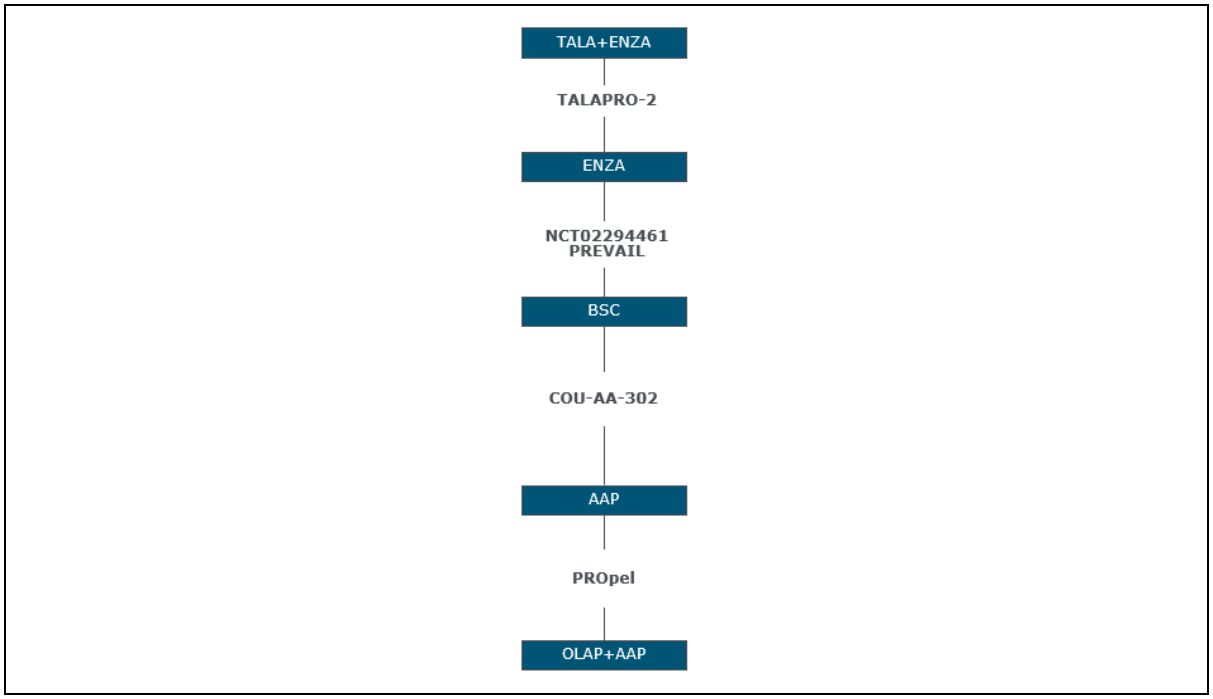
In total, eight studies were included in the NMA update, none of which were newly identified since the original NMA. New publications for these eight studies, identified in the June 2024 SLR update, were assessed to identify the availability of additional relevant data published since the original SLR. A summary of the studies included the NMA update, as well as the interventions evaluated, is displayed in **Table 15**. The restricted networks in the NMA update are presented in **Figure 7**–**Figure 10**.

Table 15: Summary of the trials used to carry out the NMA update

Trial	Intervention				
	TALA +ENZA	AAP	BSC	ENZA	OLAP +AAP
TALAPRO-2 (NCT03395197)	✓			✓	
BRCAAway (NCT03012321)		✓			✓
COU-AA-301 (NCT00638690) / COU-AA-302 (NCT00887198)		✓	✓		
NCT01591122		✓	✓		
NCT02294461			✓	✓	
NR (Hu 2020)		✓	✓		
PREVAIL			✓	✓	
PROpel (NCT03732820)		✓			✓

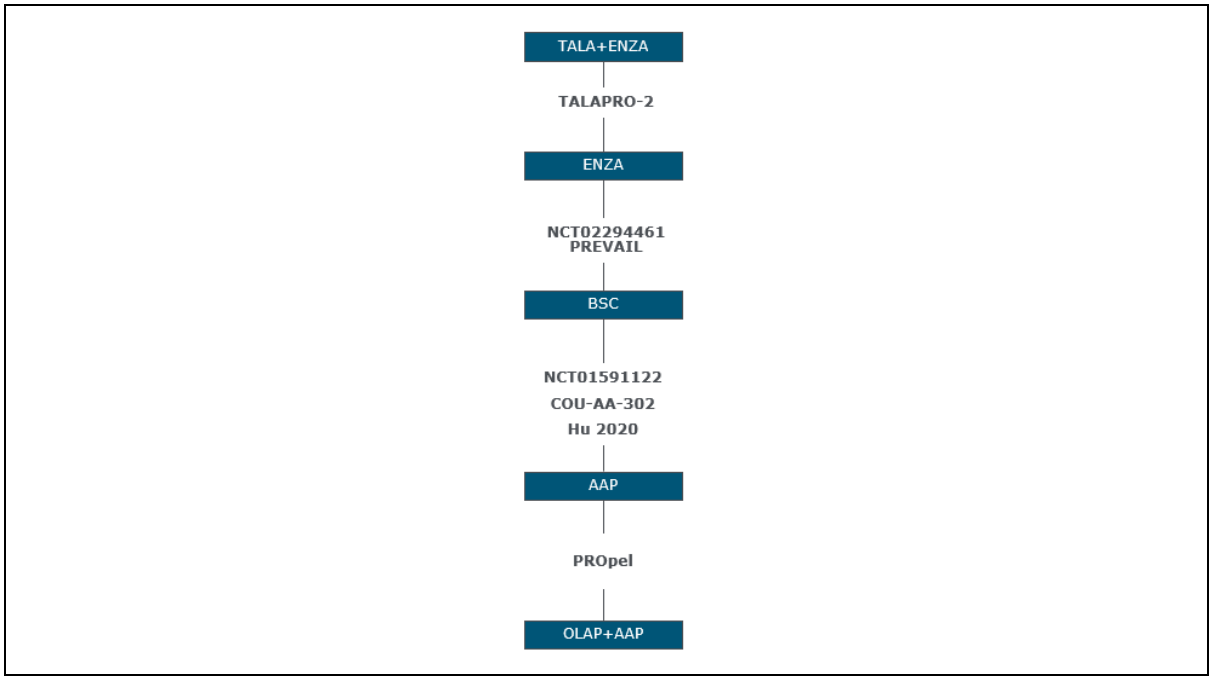
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); ENZA – Enzalutamide 160 mg PO QD; NMA – Network meta-analysis; OLAP – Olaparib 300 mg PO BID; TALA – Talazoparib 0.5 mg QD

Figure 7: rPFS and OS network (N=5)



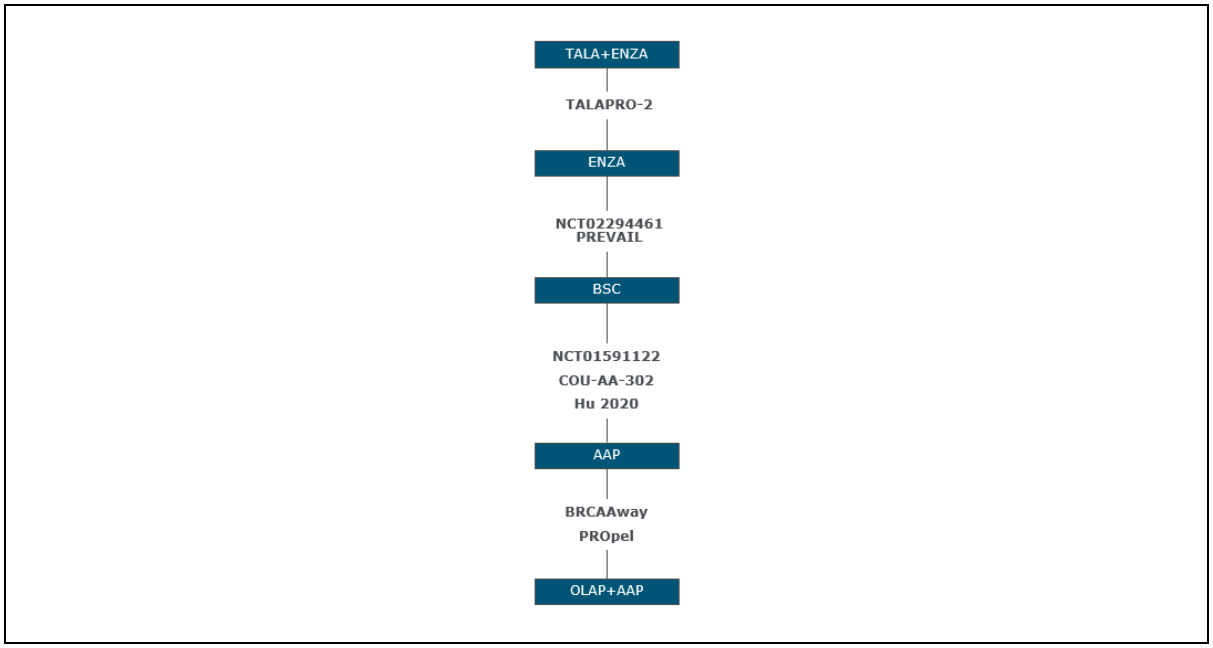
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); ENZA – Enzalutamide 160 mg PO QD; OLAP – Olaparib 300 mg PO BID; OS – Overall survival; rPFS – Radiographic progression-free survival; TALA – Talazoparib 0.5 mg QD

Figure 8: Time to PSA network (N=7)



Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); ENZA – Enzalutamide 160 mg PO QD; OLAP – Olaparib 300 mg PO BID; PSA – Prostate-specific antigen; TALA – Talazoparib 0.5 mg QD

Figure 9: PSA response (N=8)



Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); ENZA – Enzalutamide 160 mg PO QD; OLAP – Olaparib 300 mg PO BID; PSA – Prostate-specific antigen; TALA – Talazoparib 0.5 mg QD

Figure 10: ORR network (N=5)

Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); ENZA – Enzalutamide 160 mg PO QD; OLAP – Olaparib 300 mg PO BID; ORR – Objective response rate; TALA – Talazoparib 0.5 mg QD

B.3.9.2 NMA methodology

An NMA was conducted to allow simultaneous synthesis and inference regarding the comparative effectiveness of talazoparib with enzalutamide against olaparib with abiraterone for the outcomes of interest (including those relevant to the NICE scope): rPFS, OS, time to PSA, PSA response, and ORR.

An NMA is an extension of a standard pairwise meta-analysis that coherently summarises all direct and indirect evidence about treatment effects and allows a simultaneous comparison to be made between all pairs of treatments.[63]

The methodology described below was recommended and ratified by a statistician from Sheffield Centre for Health and Related Research (SCHARR).

B.3.9.2.1 Statistical model for the NMA

NMAs were conducted for all outcomes of interest using a Bayesian framework as described in the NICE Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) series.[63] Results are presented assuming a random effect (RE) model.

For time-to-event outcomes (rPFS, OS, time to PSA), a normal distribution was assumed for the treatment effect (log-HRs) reported within each study. For binary outcomes (PSA response, and ORR), the data generation process is assumed to follow a Binomial likelihood. The probabilities are modelled using a logit link function. Conventional $N(0, 100^2)$ reference prior distributions were used for the treatment effects and study-specific baselines.

Due to the sparsity of the networks with insufficient sample data to inform the between-study standard deviation of treatment effects, an informative prior distribution was used for the between-trial variance ($\tau^2 \sim \log\text{normal}\,[-3.95, 1.92^2]$) as recommended for meta-analyses in a general healthcare setting.[64] Alternative prior distributions were also considered where appropriate (a more precise prior for pharmaceutical versus pharmaceutical interventions; cause-specific mortality/major morbidity event: $\tau^2 \sim \log\text{normal}\,[-3.95, 1.92^2]$ as well as uninformative reference priors; **Table 26**). Results of these alternative analyses are not presented in full; only the chosen analysis is provided in this submission. The model fit and heterogeneity

of each prior distribution option are summarised in **Section B.3.9.5**, where the model selection is justified.

All analyses were conducted in the freely available software package R, using the multinma R package, which estimates parameters in a Bayesian framework using stan.[65–67] For all analyses, inference was based on four chains, each with 1000 draws after a warmup of 1000 iterations. Convergence to the target posterior distribution was assessed using Rhat and the effective sample size. Convergence was achieved without the need for thinning, avoiding data waste; the default thinning setting of 0 was applied.

The absolute goodness-of-fit was checked by comparing the total residual deviance to the total number of data points included in an analysis. Possible inconsistency between the direct and indirect evidence was not assessed due to the absence of feedback loops in the network.

Results are presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). The 95% PrI indicates the extent of between-study heterogeneity by illustrating the range of HRs that might be expected in a future study. Probabilities of treatment rankings were computed by counting the proportion of iterations of the Markov chain in which each intervention had each rank.

The estimated between-study standard deviation, τ, for each analysis is also presented. Values below 0.05 indicate low heterogeneity. Values between 0.05 and 0.5 indicate moderate heterogeneity. Values between 0.5 and 1.0 indicate high heterogeneity. Values above 1.0 indicate extremely high heterogeneity.

B.3.9.3 NMA results

The main results for each outcome are summarised below, with additional results on model fit and heterogeneity estimates shown in **Section B.3.9.4**. The primary focus of the analyses was to demonstrate similar efficacy between talazoparib with enzalutamide and olaparib with abiraterone (referred to as TALA+ENZA and OLAP+AAP, respectively, in this section).

For all outcomes (rPFS, OS, time to PSA, PSA response, ORR), TALA+ENZA had [redacted], suggesting that [redacted] in the analysis. For all outcomes, TALA+ENZA was associated with [redacted] OLAP+AAP, suggesting [redacted] efficacy.

B.3.9.3.1 rPFS

A total of five studies contributed to the analysis for rPFS. The effects of each treatment relative to BSC and TALA+ENZA are shown in **Table 16** and **Table 17**, respectively. A forest plot of the HR for the effect of each treatment relative to TALA+ENZA is shown in **Figure 11**.

TALA+ENZA was associated with [redacted] in rPFS relative to OLAP+AAP (median HR [redacted]; reciprocal of values presented in **Table 17**).

Table 16: Summary of treatment effects vs BSC for rPFS

Active treatment	HR vs BSC		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
AAP	[redacted]					
ENZA	[redacted]					
OLAP+AAP	[redacted]					
TALA+ENZA	[redacted]					

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the HR.
The reference treatment for this table is BSC. A HR>1 indicates inferiority to BSC.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; PrI – Prediction interval; rPFS – Radiographic progression-free survival; TALA – Talazoparib 0.5 mg QD

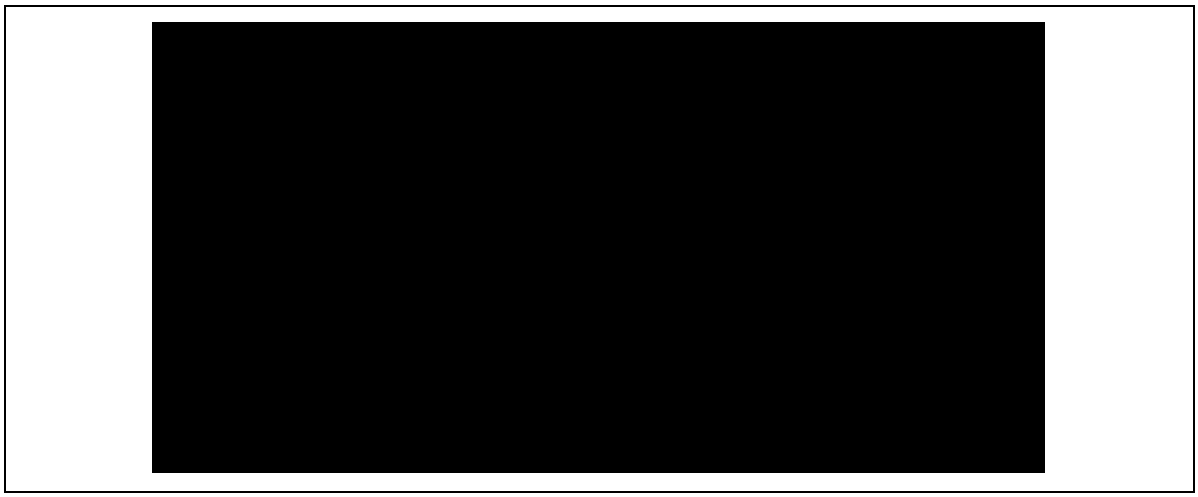
Table 17: Summary of treatment effects vs TALA+ ENZA for rPFS

Active treatment	HR vs TALA + ENZA		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
BSC	[redacted]					
AAP	[redacted]					
ENZA	[redacted]					
OLAP+AAP	[redacted]					

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the HR.
The reference treatment for this table is TALA+ENZA. A HR>1 indicates inferiority to TALA+ENZA.

Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; PrI – Prediction interval; rPFS – Radiographic progression-free survival; TALA – Talazoparib 0.5 mg QD

Figure 11: Forest plot of HR vs TALA+ENZA for rPFS



Abbreviations: AAP – Abiraterone; BSC – Best standard of care; ENZA – Enzalutamide; OLAP – Olaparib; rPFS – Radiographic progression-free survival; TALA – Talazoparib

B.3.9.3.2 OS

A total of five studies contributed to the analysis. The effects of each treatment relative to BSC and TALA+ENZA are shown in **Table 18** and **Table 19**, respectively. A forest plot of the HR for the effect of each treatment relative to TALA+ENZA is shown in **Figure 12**.

TALA+ENZA was associated with [redacted] in OS relative OLAP+AAP (median HR [redacted]; reciprocal of values presented in **Table 19**).

Table 18: Summary of treatment effects vs BSC for OS

Active treatment	HR vs BSC		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAP+AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TALA+ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the HR.
The reference treatment for this table is BSC. A HR>1 indicates inferiority to BSC.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; OS – Overall survival; PrI – Prediction interval; TALA – Talazoparib 0.5 mg QD

Table 19: Summary of treatment effects vs TALA+ ENZA for OS

Active treatment	HR vs TALA + ENZA		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAP+AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the HR.
The reference treatment for this table is TALA+ENZA. A HR>1 indicates inferiority to TALA+ENZA.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; OS – Overall survival; PrI – Prediction interval; TALA – Talazoparib 0.5 mg QD

Figure 12: Forest plot of HR vs TALA+ENZA for OS

Abbreviations: AAP – Abiraterone; BSC – Best standard of care; ENZA – Enzalutamide; OLAP – Olaparib; OS – Overall survival; TALA – Talazoparib

B.3.9.3.3 Time to PSA

A total of seven studies contributed to the analysis for time to PSA progression. The effects of each treatment relative to BSC and TALA+ENZA are shown in **Table 20** and **Table 21**, respectively. A forest plot of the HR for the effect of each treatment relative to TALA+ENZA is shown in **Figure 13**.

TALA+ENZA was associated with [redacted] relative to OLAP+AAP (median HR [redacted]; reciprocal of values presented in **Table 21**).

Table 20: Summary of treatment effects vs BSC for time to PSA progression

Active treatment	HR vs BSC		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAP+AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TALA+ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the HR.
The reference treatment for this table is BSC. A HR>1 indicates inferiority to BSC.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; PrI – Prediction interval; PSA – Prostate specific antigen; TALA – Talazoparib 0.5 mg QD

Table 21: Summary of treatment effects vs TALA+ ENZA for time to PSA progression

Active treatment	HR vs TALA + ENZA		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAP+AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the HR.
The reference treatment for this table is TALA+ENZA. A HR>1 indicates inferiority to TALA+ENZA.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; PrI – Prediction interval; PSA – Prostate specific antigen; TALA – Talazoparib 0.5 mg QD

Figure 13: Forest plot of HR vs TALA+ENZA for time to PSA response

Abbreviations: AAP – Abiraterone; BSC – Best standard of care; ENZA – Enzalutamide; OLAP – Olaparib; PSA – Prostate specific antigen; TALA – Talazoparib

B.3.9.3.4 PSA response

A total of eight studies contributed to the analysis for PSA response. The effects of each treatment relative to BSC and TALA+ENZA are shown in **Table 22** and **Table 23**, respectively. A forest plot of the OR for the effect of each treatment relative to TALA+ENZA is shown in **Figure 14**.

TALA+ENZA was associated with [redacted] relative to OLAP+AAP (median OR: [redacted]; reciprocal of values presented in **Table 23**).

Table 22: Summary of treatment effects vs BSC for PSA response

Active treatment	OR vs BSC		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
AAP	[redacted]					
ENZA						
OLAP+AAP						
TALA+ENZA						

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the OR.
The reference treatment for this table is BSC. A OR>1 indicates superiority to BSC.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; PrI – Prediction interval; PSA – Prostate specific antigen; TALA – Talazoparib 0.5 mg QD

Table 23: Summary of treatment effects vs TALA + ENZA for PSA response

Active treatment	OR vs TALA + ENZA		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
BSC	[redacted]					
AAP						
ENZA						
OLAP+AAP						

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the OR.
The reference treatment for this table is TALA+ENZA. A OR>1 indicates superiority to TALA+ENZA.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; PrI – Prediction interval; PSA – Prostate specific antigen; TALA – Talazoparib 0.5 mg QD

Figure 14: Forest plot for PSA response vs TALA+ENZA for PSA response

Abbreviations: AAP – Abiraterone; BSC – Best standard of care; ENZA – Enzalutamide; OLAP – Olaparib; PSA – Prostate specific antigen; TALA – Talazoparib

B.3.9.3.5 ORR

A total of six studies contributed to the analysis for ORR. The effects of each treatment relative to BSC and TALA+ENZA are shown in **Table 24** and **Table 25**, respectively. A forest plot of the OR for the effect of each treatment relative to TALA+ENZA is shown in **Figure 15**.

TALA+ENZA was associated with [redacted] relative to OLAP+AAP (median OR: [redacted]; reciprocal of values presented in **Table 23**).

Table 24: Summary of treatment effects vs BSC for ORR

Active treatment	OR vs BSC		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				
AAP	[redacted]					
ENZA						
OLAP+AAP						
TALA+ENZA						

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the OR.
The reference treatment for this table is BSC. A OR>1 indicates superiority to BSC.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; ORR – Overall response rate; PrI – Prediction interval; TALA – Talazoparib 0.5 mg QD

Table 25: Summary of treatment effects vs TALA+ ENZA for ORR

Active treatment	OR vs BSC		95% CrI	95% PrI	Mean rank	P(best)
	Mean	Median				

BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLAP+AAP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NMA results are not statistically significant if the lower/upper CrI include the value 1 for the OR.
The reference treatment for this table is TALA+ENZA. A OR>1 indicates superiority to TALA+ENZA.
Abbreviations: AAP – Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC – Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and Prednisolone 5 mg PO BID); CrI – Credible interval; ENZA – Enzalutamide 160 mg PO QD; HR – Hazard ratio; OLAP – Olaparib 300 mg PO BID; ORR – Overall response rate; PrI – Prediction interval; TALA – Talazoparib 0.5 mg QD

Figure 15: Forest plot of OR vs TALA+ENZA for ORR

Abbreviations: AAP – Abiraterone; BSC – Best standard of care; ENZA – Enzalutamide; OLAP – Olaparib; ORR – Overall response rate; TALA – Talazoparib 0.5 mg QD

B.3.9.4 Statistical assessment of heterogeneity

Table 26 displays the assessment of model fit and heterogeneity for all time-to-event and binary outcomes. For each outcome, at least two models were tested, based on different priors and/or a different number of trial inputs. The most suitable model was selected based on the total residual deviance, deviance information criterion (DIC), and between-study standard deviation. For all three of these parameters, a smaller value indicates a better model fit.

Total residual deviance, DIC, and between-study SD were [redacted] across the studies as shown by **Table 26**. The between-study SD for most of the selected models was between [redacted] and [redacted], indicating [redacted]. Assessing all the outcomes, the

[redacted] prior model was selected as the most appropriate fit for the data, to optimise these three measures across all outcomes. This is the model presented in this submission.

Table 26: Model fit and heterogeneity for all analyses

Analysis			Absolute model fit		DIC	Between-study SD (95% CrI)
Outcome variable	N	Prior	Total residual deviance	Data points		
rPFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS	[redacted]	[redacted]	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to PSA response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSA response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results in green indicate primary analyses presented in submission.

Abbreviations: CrI – Credible intervals; DIC – Deviance information criterion; ORR – Overall response rate; OS – Overall survival; PSA – Prostate-specific antigen; rPFS – Radiographic progression-free survival; SD – Standard deviation

B.3.9.5 Uncertainties in the indirect and mixed treatment comparisons and sensitivity analyses

The NMA analyses were based on best practices, in line with the recommendations of the NICE DSU,[63] using publicly available code to ensure transparency and reproducibility. The methodology for the analysis was also recommended and ratified by a statistician from SCHARR.

The feasibility assessment evaluated trial characteristics, eligibility criteria, baseline characteristics, and outcome characteristics of all the studies included in the NMA. Two limitations were identified. Firstly, the BRCAAway study is phase 2 and unblinded, misaligning with all other studies in the network, which were blinded

phase 3 studies. Despite being a limitation of the analysis, this heterogeneity is not expected to materially impact the results of the NMA because the PROpel study also provides data for the same comparators as BRCAAway (i.e., the same link in the network).

Secondly, there is heterogeneity relative to the rest of the network for the follow-up time for the binary outcomes (PSA response, ORR) in studies NCT01591122 and NCT02294461.

To account for the sources of heterogeneity, sensitivity analyses were explored, one in which the two studies were excluded from the network and one accounting for study duration. Results of the sensitivity analyses (see **Appendix J**) [redacted] with the base case, [redacted]. In addition, to account for heterogeneity and within-study and between-study variability, a random effects model was used for the NMA. By accounting for between-study variability, using random effects reflects a more conservative approach than fixed effects, and applies a higher threshold for statistical significance.

The validity of NMAs is dependent on adequate balance or adjustment for TEMs that differ between trials. To ensure constancy in expectation of random effects, it is important to capture all relevant TEMs for the disease area and to assess the balance between studies via a feasibility assessment. NMAs require the assumption of constancy of relative effects on a linear scale. This assumption is relaxed to constancy in expectation for random effects, as applied in the analysis for this NICE appraisal. Potential TEMs were identified through a review of the published literature and in consultation with clinical experts.[7] No issues were identified in the balance of prognostic factors or treatment effect modifiers. However, given the NMA relies on summary data, adequate adjustment for differences in TEMs between studies may not be possible.

A superiority analysis was chosen over a non-inferiority analysis as the most appropriate approach for this NMA based on advice from a statistician at SCHARR, the absence a NICE user guide recommendation to the contrary, and the consideration that lack of statistical significance in demonstrating superiority is considered evidence of similar efficacy. In this instance, the results consistently and

clearly show that TALA+ENZA is [redacted] OLA+ABI across all outcomes.

B.3.10 Adverse reactions

The AE profile of talazoparib with enzalutamide in the TALAPRO-2 trial was consistent with the known safety profiles of each agent used as monotherapy.

B.3.10.1 Extent of exposure

A summary of exposure to the study drugs for the Cohort 1 Part 2 all-comers safety population is presented in

Table 27. At the data cutoff date of 16 August 2022 (median follow-up for the primary analysis: 24.9 months for the talazoparib arm, 24.6 months for the placebo arm), the median duration of treatment was 86.00 weeks for talazoparib and 69.86 weeks for placebo, with a median relative dose intensity of 83.54% (range: 17.66–104.49%) and 100.00% (range: 53.49–142.86%), respectively.[50,51] The median duration of treatment for enzalutamide was 96.57 weeks and 72.00 weeks in the talazoparib and placebo arms, respectively (median relative dose intensity: 99.87% vs 100.0%).[50]

Table 27: TALAPRO-2: Summary of the drug dosing exposure for the Cohort 1 Part 2 all-comers safety population (N=799)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)	Total (n=799)
Duration of treatment,[a] weeks			
N	397	400	797
Mean (SD)	79.83 (46.86)	71.67 (45.46)	75.74 (46.31)
Median (range)	86.00 (0.29, 186.14)	69.86 (2.14, 182.00)	74.57 (0.29, 186.14)
Relative dose intensity[b] (%)			
Mean (SD)	79.94 (21.51)	97.85 (7.66)	88.93 (18.44)
Median (range)	83.54 (17.66, 104.49)	100.00 (53.49, 142.86)	99.87 (17.66, 142.86)
Dose interruptions, n (%)	268 (67.3)	134 (33.4)	402 (50.3)
Due to AE	235 (59.0)	68 (17.0)	303 (37.9)
Due to other reasons	110 (27.6)	80 (20.0)	190 (23.8)
Dose reductions, n (%)	218 (54.8)	45 (11.2)	263 (32.9)
Due to AE	209 (52.5)	28 (7.0)	237 (29.7)
Due to other reasons	13 (3.3)	11 (2.7)	24 (3.0)

[a] Treatment duration (weeks) is defined as (date of last dose – date of first dose +1)/7.
[b] Relative dose intensity (%) is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in %.
Abbreviations: AE – Adverse event; SD – Standard deviation
Source: TALAPRO-2 CSR - Table 18[50]

B.3.10.2 Overview of adverse events

Table 28 displays the AEs observed in the TALAPRO-2 Cohort 1 Part 2 all-comers safety population from the time of the first dose of study treatment through to 28 days after permanent discontinuation of all study treatments or before initiation of a new antineoplastic or any investigational therapy, whichever occurred first.[50]

The rate of treatment-emergent adverse events (TEAEs) was similar for the talazoparib and placebo arms (98% vs 95%), but the talazoparib arm was associated with a higher rate of grade ≥3 TEAEs (75% vs 45%), treatment-related AEs (90% vs 70%), and treatment-related grade ≥3 TEAEs (59% vs 18%).[50,51]

The most common all-cause AEs of any grade in the talazoparib arm (≥30% of patients) were anaemia, neutropenia, and fatigue.[50] The most common grade 3-4 AEs (≥10% of patients) in the talazoparib arm were anaemia (46%) and neutropenia (18%).[50]

There were more dose interruptions and reductions due to AEs in the talazoparib arm than in the placebo arm.[50] The most common AEs leading to a dose reduction of talazoparib were anaemia (43%), neutropenia (15%), thrombocytopenia (6%), and leukopenia (2%).[50] The most common AEs leading to discontinuation of talazoparib were anaemia (8%) and neutropenia (3%).[50] Discontinuation rates of enzalutamide due to AEs were 11% in the talazoparib arm versus 11% in the placebo arm.[50]

Table 28: Summary of TEAEs for the Cohort 1 Part 2 all-comers safety population (N=799)

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any AE (%)	392 (98)	299 (75)	379 (95)	181 (45)
Treatment-related AE (%)	357 (90)	234 (59)	279 (70)	71 (18)
Serious AE (%)	157 (39)	145 (36)	107 (27)	94 (23)
Serious and treatment-related AE (%)	78 (20)	68 (17)	12 (3)	11 (3)
AE resulting in dose interruption of:				
Talazoparib or placebo[a] (%)	247 (62)	-	84 (21)	-
Enzalutamide[b] (%)	156 (39)	-	78 (19)	-
AE resulting in dose reduction of:				
Talazoparib or placebo[a] (%)	210 (53)	-	27 (7)	-
Enzalutamide[b] (%)	58 (15)	-	32 (8)	-
AE resulting in permanent drug discontinuation of:				
Talazoparib or placebo[a] (%)	75 (19)	-	49 (12)	-
Enzalutamide[b] (%)	43 (11)	-	44 (11)	-
Grade 5 AE (%)	13 (3)[c]	-	18 (4)[d]	-
Most common AE (all grades in ≥10% of patients)[e] (%)				
Anaemia	262 (66)	185 (46)	70 (17)	17 (4)
Neutropenia	142 (36)	73 (18)	28 (7)	6 (1)
Fatigue	134 (34)	16 (4)	118 (29)	8 (2)
Thrombocytopenia	98 (25)	29 (7)	14 (3)	4 (1)
Back pain	88 (22)	10 (3)	72 (18)	4 (1)
Leukopenia	88 (22)	25 (6)	18 (4)	0
Decreased appetite	86 (22)	5 (1)	63 (16)	4 (1)
Nausea	82 (21)	2 (<1)	50 (12)	3 (<1)

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Constipation	72 (18)	1 (<1)	68 (17)	2 (<1)
Fall	71 (18)	9 (2)	59 (15)	8 (2)
Arthralgia	58 (15)	2 (<1)	79 (20)	2 (<1)
Asthenia	57 (14)	11 (3)	38 (9)	3 (<1)
Diarrhoea	57 (14)	1 (<1)	55 (14)	0
Hypertension	55 (14)	21 (5)	62 (15)	30 (7)
Dizziness	48 (12)	4 (1)	23 (6)[f]	2 (<1)
Hot flush	47 (12)	0	53 (13)[f]	0
Lymphopenia	45 (11)	20 (5)	20 (5)	4 (1)
Oedema peripheral	42 (11)	0	23 (6)[f]	0
Dyspnoea	41 (10)	2 (<1)	25 (6)	1 (<1)
Decreased weight	40 (10)	2 (<1)	33 (8)	3 (<1)

Data are n(%). Shown are AEs that occurred from the time of the first dose of study treatment through to 28 days after permanent discontinuation of all study treatments or before initiation of a new antineoplastic or any investigational therapy, whichever occurred first. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[a] Includes permanent discontinuation, dose reduction, or dose interruption of talazoparib or placebo with permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide.

[b] Includes permanent discontinuation, dose reduction, or dose interruption of enzalutamide only plus permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide.

[c] None were considered treatment-related.

[d] Two were considered treatment-related.

[e] None of these events were recorded as grade 5.

[f] One additional patient in each of these categories had a missing or unknown grade.

Abbreviations: TEAE – Treatment-emergent adverse event

Source: Agarwal et al 2023 - Table 3[51]

B.3.10.3 SAEs

Table 29 reports the serious adverse events (SAEs) in the Cohort 1 Part 2 all-comers safety population. SAEs were reported [redacted] for participants in the talazoparib with enzalutamide treatment arm than for participants in the placebo with enzalutamide treatment arm.[50] [redacted], observed in [redacted] and [redacted] of participants in the talazoparib arm and placebo arm, respectively.[50]

Table 29: Summary of SAEs for the Cohort 1 Part 2 all-comers safety population (N=799)

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any SAE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia (%)	[redacted]	[redacted]	[redacted]	[redacted]
Haematuria (%)	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection (%)	[redacted]	[redacted]	[redacted]	[redacted]

Participants reporting more than one AE within a preferred term are counted only once in that preferred term. For participants reporting more than one AE within a system organ class or preferred term, the AE with maximum grade is included in the table. The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systematic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.

Abbreviations: SAE – Serious adverse event

Source: TALAPRO-2 CSR - Table 55[50]

B.3.10.4 SREs

Table 30 reports the SREs in the Cohort 1 Part 2 all-comers safety population. SREs were reported [redacted] for participants in the talazoparib with enzalutamide treatment arm than for participants in the placebo with enzalutamide treatment arm.[50] [redacted], observed in [redacted] and [redacted] of participants in the talazoparib arm and placebo arm, respectively.[50]

Table 30: Summary of SREs for the Cohort 1 Part 2 all-comers safety population (N=799)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)
Any SRE (%)	[redacted]	[redacted]
Non-symptomatic fracture (%)	[redacted]	[redacted]
Radiotherapy to bone (%)	[redacted]	[redacted]
Spinal cord compression (%)	[redacted]	[redacted]
Surgery to bone (%)	[redacted]	[redacted]
Symptomatic fracture (%)	[redacted]	[redacted]

Participants are only counted once per treatment event. MedDRA v25 coding dictionary applied.

Abbreviations: SRE – Skeletal related event

Source: TALAPRO-2 CSR - Table 63[50]

B.3.11 Conclusions about comparable health benefits and safety

As specified in the decision problem and NICE scope, this submission presents a cost comparison between talazoparib with enzalutamide and olaparib with

abiraterone, on the basis of equivalent mechanisms of action, similar health benefits, equivalent target population, and lower costs (see **Section B.1.1** for details).

In the absence of head-to-head clinical data between talazoparib with enzalutamide and olaparib with abiraterone, an NMA was conducted to estimate comparative efficacy (see **Section B.3.9.2** for details). For all NMA-reported outcomes (rPFS, OS, time to PSA, PSA response, and ORR), talazoparib with enzalutamide was associated with [redacted] against olaparib with abiraterone (see **Section B.3.9.3** for details), [redacted]. In addition, both combinations consist of a PARP inhibitor and an NHA, highlighting similar mechanism of action. UK clinical experts have also indicated that both combinations have similar clinical efficacies and that they don't see any difference in the side effect profiles of the two PARP inhibitors.[7] This supports the conclusion that the combinations are clinically and biologically similar. The safety profile of talazoparib plus enzalutamide in the TALAPRO-2 trial is consistent with the established safety profiles of the individual medications.

During the TALAPRO-2 trial, 43.5% patients developed grade 3 anaemia and 3.3% developed grade 4 anaemia.[50] However, anaemia was not a cumulative toxicity and the steepest reduction in Hb was noted within the first 13 weeks, with a median time to onset of 3.3m.[51,68] The trial protocol did not require dose reduction or interruption of talazoparib until anaemia was grade 3 or higher (haemoglobin <8 g/dL).[51] Furthermore, 49% of patients had grade 1-2 anaemia upon entry to the trial. Anaemia was managed in a number of ways, including dose modification (42.5%) and blood transfusions (39.2%).[50,51] After protocol-mandated dose reduction only 8% discontinued due to anaemia.[51] Extrapolating these clinical trial findings into UK real-world practice, clinical experts have noted that the trial protocol did not require dose reduction or interruption of talazoparib or placebo until anaemia was grade 3 or higher (haemoglobin <8 g/dL). In reality, patients would be monitored to enable earlier intervention when signs/symptoms of anaemia are identified, thus minimising the severity of anaemia and the need for transfusion. This could be facilitated through careful monitoring of blood counts during initial 3-4 months when the risk of anaemia is the greatest. Although it is acknowledged anaemia is the most common TRAE, UK clinical experts believe that the burden of anaemia in real-life practice will

not be comparable to that observed within the TALAPRO-2 trial and it is predominately manageable on an outpatient basis.

B.3.12 Ongoing studies

TALAPRO-2 represents the only ongoing trial assessing the efficacy and safety of talazoparib with enzalutamide in mCRPC. Data presented in this submission are from the pre-planned primary analysis of Part 2 of TALAPRO-2, with a data cutoff on 16th August 2022 (median follow-up for the primary analysis: 24.9 months for the talazoparib arm, 24.6 months for the placebo arm).

The final analysis for the secondary endpoints in Part 2 has not yet been conducted.

B.4 Cost comparison analysis

B.4.1 Changes in service provision and management

No changes in service provision and management are expected following introduction of talazoparib with enzalutamide. Talazoparib with enzalutamide is a combination regimen of once-daily oral tablets for treating patients with mCRPC for whom chemotherapy is not clinically indicated.[1] The mode of administration is consistent with other currently available treatment options (olaparib, abiraterone, enzalutamide) licensed for the same indication.[12,72,73] Talazoparib with enzalutamide will be prescribed in secondary care with routine follow-up in secondary care. As talazoparib with enzalutamide is licensed for the full population, regardless of biomarker status, no specific genetic testing is required.

Healthcare resource items utilised during monitoring with talazoparib with enzalutamide (**Section B.4.2.3**) include outpatient visits (consultant-led), computed tomography (CT) scans, bone scans, full blood counts, and PSA tests.[1, 4,12] Healthcare resource use with talazoparib with enzalutamide is expected to be lower than with olaparib with abiraterone because olaparib with abiraterone also requires liver function tests, kidney function tests, and treatment toxicity monitoring.[4]

B.4.2 Cost comparison analysis inputs and assumptions

B.4.2.1 Features of the cost comparison analysis

A cost comparison analysis was developed from the perspective of the NHS and PSS in England and Wales to evaluate the expected costs of talazoparib with enzalutamide versus olaparib with abiraterone in patients with mCRPC for whom chemotherapy is not clinically indicated. The analysis was conducted under the assumptions of similar clinical efficacy and safety.

Cost inputs considered in the base case analysis include drug acquisition costs and monitoring costs. It was assumed that there are no administration costs associated with oral drugs. AE and SRE management costs were also excluded in the base case, in line with the assumption of similar health benefits (see **Section B.3.11**), but were examined in scenario analyses.

Costs were calculated over a lifetime time horizon (assumed to be 30 years based on the median age of 71 years in TALAPRO-2)[51], which is considered long enough to capture the difference in costs of treatment for patients with mCPRC, as per NICE guidelines.[2] Alternative time horizons of 10 and 20 years were explored in scenario analyses. A model cycle length of 30 days was chosen, and, in line with the TA951 submission[46], a mid-cycle correction was not applied in the base case. The impact of mid-cycle correction on the results was examined in a scenario analysis. Discounting was not applied in the base case as per NICE guidelines for cost comparisons;[2] however, a 3.5% discount on future costs was explored in a scenario analysis.

Unit costs were sourced from the British National Formulary (BNF; 2024),[74] the electronic Market Information Tool (eMIT) National Database (2023),[75] and the National Schedule of NHS Costs (2021-2022).[76] The ONS Health CPI Index was adopted for the inflation to 2024 costs in the model.

B.4.2.2 Intervention and comparators' acquisition costs

A summary of acquisition costs of talazoparib with enzalutamide and olaparib with abiraterone used in the cost comparison analysis is presented in **Table 31**. The existing PAS price of [redacted] per 30-tablet pack is used for talazoparib, which equates to a simple discount on the list price of [redacted]. For olaparib, the list price is used given that the PAS price is confidential and therefore not available to the company. The list price was also used for enzalutamide and abiraterone. The dose and posology for each drug was based on their respective SmPC.[14,71] Due to the clinical equivalence assumed between talazoparib with enzalutamide and olaparib with abiraterone and because all aforementioned drugs are administered orally, patients were assumed to receive 100% of their targeted dose for each regimen component. It is unclear if comparator confidential prices have simple or complex agreements in place. If a complex agreement is in place, the company believes that the committee should consider scenarios with the actual price being paid in the NHS alongside any potential commercial arrangements.

Table 31: Acquisition costs of talazoparib with enzalutamide and olaparib with abiraterone used in the cost comparison analysis

	Talazoparib with enzalutamide		Olaparib with abiraterone		
	Talazoparib	**Enzalutamide**	**Olaparib**	**Abiraterone**	**Prednisolone**
Pharmaceutical formulation[74]	0.25 mg tablets in 30 tablets pack	40 mg tablets in 112 tablets pack	150 mg tablets in 56 tablets pack	500 mg tablets in 56 tablets pack	5 mg tablets in 28 tablets pack
(Anticipated) care setting	Secondary care				
Acquisition cost per pack (excluding VAT)[74–76]	£[redacted] (with PAS)	£2,734.67	£2,317.50	£91.60	£0.41
Method of administration[14,71]	Oral				
Dose[14,71]	0.5 mg	160 mg	300 mg	1,000 mg	5 mg
Dosing frequency[14,71]	Once daily	Once daily	Twice daily	Once daily	Twice daily
Average length of a course of treatment	Long term. Patients should be treated until disease progression or unacceptable toxicity occurs.[14,71] Duration of treatment is discussed in **Section B.4.2.6**.				
Average cost of a course of treatment (acquisition costs only)	£[redacted] (with PAS)	£2,930.00	£4,966.07	£98.14	£0.88
Average cost of a course of combination treatment (acquisition costs only)	£[redacted] (with talazoparib PAS)		£5,065.09		

Abbreviations: mg – milligram; NA – Not applicable; TBD – To be determined; VAT – Value added tax

Source: BNF (2024)[74], eMIT National Database (2023)[75], National Schedule of NHS costs (2021-2022)[76], and talazoparib and olaparib SmPCs[14,71]

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Monitoring costs were applied for the portion of time patients were receiving treatment. Frequency of resource use for each treatment regimen was based on TA951[46], as this is the most recent and best available data reviewed and accepted by NICE, as well as each drug's SmPCs.[14,71] Both treatment regimens required outpatient visits, CT scans, bone scans, full blood counts, and PSA tests; however, as mentioned in **Section B.4.1**, only olaparib with abiraterone required liver function tests, kidney function tests, and treatment toxicity monitoring.[14, 46,71] The frequency of monitoring requirements is reduced after the first 3 months of treatment, reflecting a reduced risk of treatment-related adverse events (TRAEs) after this timepoint.[46] The monitoring unit costs were sourced from the National Schedule of NHS Costs (2021-22),[76] and the costing codes were aligned with the TA951 submission.[46]

Summaries of monitoring requirements and costs for each treatment are presented in **Table 32** and **Table 33**, respectively.

Table 32: Monitoring requirements of talazoparib with enzalutamide and olaparib with abiraterone

	Talazoparib with enzalutamide				Olaparib with abiraterone			
	First 3 months		4+ months		First 3 months		4+ months	
Resource required	**% of patients per month**	**Frequency per month**	**% of patients per month**	**Frequency per month**	**% of patients per month**	**Frequency per month**	**% of patients per month**	**Frequency per month**
Outpatient visit (consultant led)	50%	2.175	50%	1.088	50%	2.175	50%	1.088
CT scan	100%	2.175	100%	2.175	100%	2.175	100%	2.175
Bone scan	20%	0.348	20%	0.348	20%	0.348	20%	0.348
Full blood count	100%	1	100%	1	100%	2.175	100%	1.088
Liver function test	0%	0	0%	0	100%	2.175	100%	1.088
Kidney function test	0%	0	0%	0	100%	2.175	100%	1.088
Treatment toxicity monitoring (first 12 months)	0%	0	0%	0	100%	1.001	100%	1.001
PSA test	100%	2.175	100%	1.088	100%	2.175	100%	1.088

Abbreviations: CT – Computed tomography; PSA – Prostate specific antigen

Source: NICE TA951 submission[46] and talazoparib and olaparib SmPCs[14,71]

Table 33: Monitoring costs of talazoparib with enzalutamide and olaparib with abiraterone (total monthly cost)

Resource required	Talazoparib with enzalutamide		Olaparib with abiraterone		Unit cost	Unit cost sources
	First 3 months	4+ months	First 3 months	4+ months		
Outpatient visit (consultant led)	£281.03	£140.52	£281.03	£140.52	£258.42	NHS (2021-22). Service code: 370. Service description: Medical Oncology.
CT scan	£374.95	£374.95	£374.95	£374.95	£172.39	NHS (2021-22). Total HRGs. Weighted average of the currency code: RD20A, RD21A,RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, and RD27Z. Currency description: Different variations of Computerised Tomography Scan.
Bone scan	£10.62	£10.62	£10.62	£10.62	£152.56	NHS (2021-22). Total HRGs. Currency code: RN15A. Currency description: Nuclear bone scan of two or three phases, 19 years and above.
Full blood count	£3.46	£3.46	£7.53	£3.77	£3.46	NHS (2021-22). Currency code: DAPS05. Currency description: Haematology.
Liver function test	£0.00	£0.00	£3.93	£1.97	£1.81	NHS (2021-22). DAPS. Currency code: DAPS04. Currency description: Clinical biochemistry.
Kidney function test	£0.00	£0.00	£7.53	£3.77	£3.46	NHS (2021-22). Currency code: DAPS05. Currency code: Haematology.
Treatment toxicity[a]	£0.00	£0.00	£3.47	£3.47	£3.46	NICE TA951
PSA test	£3.93	£1.97	£3.93	£1.97	£1.81	NHS (2021-22). DAPS. Currency code: DAPS04. Currency description: Clinical biochemistry.
Total cost per month	£674.00	£531.52	£693.00	£541.02	--	

[a] First 12 months.

Abbreviations: CT – Computed tomography; HRG – Healthcare Resource Group; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PSA – Prostate specific antigen

Source: National Schedule of NHS costs (2021-2022)[76] and NICE TA951 submission[46]

B.4.2.4 Adverse reaction unit costs and resource use

As noted in **Section B.4.4.2** AE management costs were included in a scenario analysis only. The model accounts for the impact of grade ≥3 TRAEs occurring in ≥5% of patients receiving treatment. Incidence rates of AEs were sourced from TALAPRO-2 and PROpel for talazoparib with enzalutamide and olaparib with abiraterone treatment arms, respectively. Unit costs per event were based on the National Schedule of NHS Costs (2021-22).[76] It is assumed that all AEs occur and are resolved in the first cycle of treatment. Only AEs associated with first-line treatment were considered. A summary of the unit costs and resource use for the management of AEs is presented in **Table 34**.

Table 34: AE management costs of talazoparib with enzalutamide and olaparib with abiraterone

Treatment	Adverse event	Incidence	Resource use required	Cost	Source	Total
Talazoparib with enzalutamide	Anaemia	46.00%	Non-elective short-stay	£779.64	NHS (2021-22). Weighted average of the currency codes: SA04G, SA04H, SA04J, SA04K, and SA04L.	£491.55
	Hypertension	5.00%	Total HRG cost	£901.03	NHS (2021-22). Currency code: EB04Z. Currency description: Hypertension.	
	Leukopenia	6.00%	Outpatient visit	£258.42	NHS (2021-22). No HRG. Assumed as outpatient cost. Service code: 370. Service description: Medical oncology.	
	Lymphocytopenia	5.00%	Outpatient visit	£258.42	Assumed equal to leukopenia.	
	Neutropenia	18.00%	Outpatient visit	£258.42	NHS (2021-22). Service code: 370. Service description: Medical oncology.	
	Thrombocytopenia	5.00%	Outpatient visit	£258.42	NHS (2021-22). Service code: 370. Service description: Medical Oncology.	
Olaparib with abiraterone	Anaemia	15.10%	Non-elective short-stay	£779.64	NHS (2021-22). Weighted average of the currency codes: SA04G, SA04H, SA04J, SA04K, and SA04L.	£135.30
	Venous thromboembolic event	6.80%	Outpatient visit	£258.42	NHS (2021-22). Service code: 370. Service description: Medical Oncology.	

Abbreviations: AE – Adverse event; HRG – Healthcare resource group; NHS – National Health Service

Source: Agarwal et al 2023[51] and National Schedule of NHS costs (2021-2022)[76]

B.4.2.5 Miscellaneous unit costs and resource use

As noted in **Section B.4.4.2** SRE management costs were included in a scenario analysis only. It is currently uncertain what proportion of SREs are caused by the progression of the disease or by osteopenia. UK clinical experts suggest that, while both factors may contribute, the majority of SREs are generally driven by the progression of the disease.[7] UK clinical experts also suggest that the goal of mCRPC treatment should be to reduce the occurrence of SREs, as patients should not experience these events if the disease is being appropriately controlled.[7] It is therefore assumed that all SREs occur and are resolved in the first cycle of treatment. In addition, only SREs associated with first-line treatment were considered.

Incidence rates of SREs were sourced from TALAPRO-2 and PROpel for talazoparib with enzalutamide and olaparib with abiraterone treatment arms, respectively. Unit costs per event were based on the National Schedule of NHS Costs (2021-22)[76], in line with TA951.[46] The SRE incidence rates and management costs are presented in **Table 35**. Talazoparib with enzalutamide is associated with lower resource use utilisation compared to olaparib with abiraterone, with a total management cost of £[redacted] compared to £[redacted], respectively.

Table 35: SRE incidence and management costs of talazoparib with enzalutamide and olaparib with abiraterone

SRE	Unit cost	Talazoparib with enzalutamide		Olaparib with abiraterone		Source
		Incidence	Total cost	Incidence	Total cost	
Spinal cord compression	£7,185.44	[redacted]	£[redacted]	[redacted]	£[redacted]	NHS (2021-22). Currency code: HC28J. Currency description: Spinal Conditions without interventions, with CC Score 7+.
Radiation to bone	£844.33	[redacted]		[redacted]		NHS (2021-22). Weighted average of the currency codes: SC21Z, SC22Z, SC23Z, SC24Z, SC25Z, SC26Z, SC27Z and SC28Z. Assumed 5 fractures.
Surgery to bone	£5,229.31	[redacted]		[redacted]		NHS (2021-22). Currency code: HD39E, non-elective long stay. Currency description: Pathological fractures with CC score 8-10.
Pathologic bone fractures	£7,462.25	[redacted]		[redacted]		Based on TA951.

Abbreviations: NHS – National Health Service; SRE – Skeletal-related event

Source: Agarwal et al 2023[51], National Schedule of NHS costs (2021-2022)[76], and NICE TA951 submission[46]

B.4.2.6 Treatment duration

In accordance with its marketing authorisation, talazoparib with enzalutamide was administered until disease progression or until unacceptable toxicity.[14] rPFS data from the TALAPRO-2 trial was used as a proxy for modelling treatment duration for talazoparib with enzalutamide, as has been accepted in previous NICE oncology appraisal TA836.[79] In line with the assumption of similar health benefits, treatment duration was assumed to be equivalent between both treatment arms, and the rPFS data from the talazoparib with enzalutamide arm of TALAPRO-2 was therefore also applied to the olaparib with abiraterone arm.

To model treatment duration beyond the observed data from TALAPRPO-2, parametric distributions were fitted to the latest PFS data in line with the NICE DSU guidance.[63] Model selection was based on the following considerations:

- Ranking distributions based on their statistical goodness-of-fit to the observed data according to AIC and BIC;
- A visual inspection of the “observed vs predicted” plot. Kaplan-Meier plots were overlaid with parametric survival curves to assess the goodness-of-fit during the trial period;
- Long-term clinical plausibility of the extrapolations.

Goodness-of-fit statistics for each parametric distribution explored are presented in **Table 36** and the extrapolated curves are presented in **Figure 16**. The distribution associated with the lowest AIC and BIC values was the generalised gamma distribution; however, visual inspection suggests that it provides optimistic long-term survival estimates not aligned with feedback from UK clinical experts.[7] Therefore, based on the estimated proportion of patients alive at the 10-year and 30-year landmarks, the log-normal distribution was chosen in the base case analysis. The impact of adopting generalised gamma, log logistic, Gompertz, Weibull and exponential distributions for the extrapolation of rPFS data was examined in scenario analyses.

Treatment discontinuation was accounted for when calculating the acquisition and monitoring costs by multiplying the costs at Year 0 with the proportion of patients remaining on treatment (as per rPFS extrapolations) in a subsequent year to obtain the predicted cost for that year.

Table 36: Goodness-of-fit statistics for examined parametric distributions for rFPS extrapolation

Model	AIC	BIC	Average	Rank
Exponential	2,069.668	2,073.665	2,071.667	5
Generalised gamma	2,023.639	2,035.629	2,029.634	1
Gompertz	2,061.976	2,069.629	2,065.973	4
Log logistic	2,053.075	2,061.068	2,057.072	3
Log normal	2,039.165	2,047.158	2,043.162	2
Weibull	2,071.628	2,079.621	2,075.625	5

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion

Figure 16: rPFS extrapolated curves for examined parametric distributions

Abbreviations: KM – Kaplan-Meier

B.4.2.7 Clinical expert validation

Four UK clinical experts were interviewed in July–August 2024 and validated the following aspects of the economic analysis:[7]

- Similar clinical efficacy and safety between talazoparib with enzalutamide and olaparib with abiraterone

- Post-progression treatments are the same for talazoparib with enzalutamide and olaparib with abiraterone
- Log-normal distribution for the extrapolation of rPFS data
- SREs due to disease progression and costs applied as a one-off cost

B.4.2.8 Uncertainties in the inputs and assumptions

A summary of the assumptions made in the cost comparison analysis is presented in **Table 37**.

Table 37: Summary of assumptions made for the cost comparison analysis

Parameter	Assumption	Rationale
Time horizon	30 years, reflecting a lifetime horizon.	The median age of participants in the TALAPRO-2 trial is 71 years,[51] and therefore a 30-year time horizon is appropriate and long enough to capture the difference in costs of the drugs being compared, as per the NICE reference case.[2,46]
Resource use costs	Unit costs for monitoring requirements equivalent for talazoparib with enzalutamide and olaparib with abiraterone.	Both combination treatments are oral drugs that are prescribed in secondary care with routine follow-up in secondary care (see **Section B.4.1)**.
Treatment duration	Equivalent for talazoparib with enzalutamide and olaparib with abiraterone. Estimated using a log-normal distribution fitted to the latest TALAPRO-2 rPFS data.	The assumption that rPFS is broadly similar to treatment duration has been demonstrated in the literature and accepted in previous appraisals.[79,80] Application of the same rPFS curve to both treatment arms is in line with the assumption of similar clinical efficacy. Log-normal curve was chosen in the base-case scenario based on the clinical expert opinion, statistical fit, and visual fit.
Post-progression treatment	Patients treated with first-line talazoparib with enzalutamide or olaparib with abiraterone will receive the same treatment following progression and experience the same treatment outcomes.	Patients are expected to receive the same second-line therapy irrespective of their use of talazoparib with enzalutamide or olaparib with abiraterone as first-line therapy. This was validated by UK clinical experts who perceive no difference in the post-progression treatments for both arms.[7]
Comparator drug cost	The list price of olaparib with abiraterone was used throughout the analysis.	The PAS in place for olaparib with abiraterone is confidential and not available to the company.

Abbreviations: AE – Adverse event; NICE – National Institute for Health and Care Excellence; PAS – Patient access scheme; rPFS – Radiographic progression-free survival

B.4.3 Base-case results

The base case results show that talazoparib with enzalutamide is associated with cost savings of £[redacted] compared with olaparib with abiraterone over a 30-year time horizon (**Table 38**).

Table 38: Base case results (with PAS for intervention; list price for comparator)

Technologies	Acquisition costs	Resource costs	Total costs	Incremental costs
Talazoparib with enzalutamide	£[redacted]	£40,225	£[redacted]	[redacted]
Olaparib with abiraterone	£377,966	£40,971	£418,937	--

B.4.4 Sensitivity and scenario analyses

B.4.4.1 OWSA

A one-way sensitivity analysis (OWSA) was carried out to examine the impact of parameter uncertainty in the model, varying the following inputs by 10%:

- Cost and frequency of outpatient visit (consultant led)
- Cost and frequency of CT scan
- Cost and frequency of bone scan
- Cost and frequency of full blood count
- Cost and frequency of liver function test
- Cost and frequency of kidney function test
- Cost and frequency of treatment toxicity monitoring
- Cost and frequency of PSA test

The data inputs used in the OWSA are presented in

Table 39.

Table 39: OWSA inputs

	Parameters	Mean value	Upper bound value	Lower bound value
TALA+ ENZA (first 3 months)	Frequency of outpatient visit (consultant led)	1.0875	0.9788	1.1963
	Frequency of CT scan	2.1750	1.9575	2.3952
	Frequency of bone scan	0.0696	0.0626	0.0766
	Frequency of full blood count	1	0.9000	1.1000
	Frequency of liver function test	0	0	0
	Frequency of kidney function test	0	0	0
	Frequency of treatment toxicity monitoring	0	0	0
	Frequency of PSA test	2.1750	1.9575	2.3925
TALA+ ENZA (4+ months)	Frequency of outpatient visit (consultant led)	0.5438	0.4894	0.5981
	Frequency of CT scan	2.1750	1.9575	2.3925
	Frequency of bone scan	0.0696	0.0626	0.0766
	Frequency of full blood count	1	0.9000	1.1000
	Frequency of liver function test	0	0	0
	Frequency of kidney function test	0	0	0
	Frequency of treatment toxicity monitoring	0	0	0
	Frequency of PSA test	1.0875	0.9788	1.1963
OLAP+AAP (first 3 months)	Frequency of outpatient visit (consultant led)	1.0875	0.9788	1.1963
	Frequency of CT scan	2.1750	1.9575	2.3925
	Frequency of bone scan	0.0696	0.0626	0.0766
	Frequency of full blood count	2.1750	1.9575	2.3925
	Frequency of liver function test	2.1750	1.9575	2.3925
	Frequency of kidney function test	2.1750	1.9575	2.3925
	Frequency of treatment toxicity monitoring	1.0005	0.9005	1.1006
	Frequency of PSA test	2.1750	1.9575	2.3925
OLAP+AAP (4+ months)	Frequency of outpatient visit (consultant led)	0.5438	0.4894	0.5981
	Frequency of CT scan	2.1750	1.9575	2.3925
	Frequency of bone scan	0.0696	0.0626	0.0766
	Frequency of full blood count	1.0875	0.9788	1.1963
	Frequency of liver function test	1.0875	0.9788	1.1963
	Frequency of kidney function test	1.0875	0.9788	1.1963
	Frequency of treatment toxicity monitoring	1.0005	0.9005	1.1006
	Frequency of PSA test	1.0875	0.9788	1.1963

	Parameters	Mean value	Upper bound value	Lower bound value
Costs	Cost of outpatient visit (consultant led)	£258.42	£232.58	£284.26
	Cost of CT scan	£172.39	£155.15	£189.63
	Cost of bone scan	£152.56	£137.30	£167.82
	Cost of full blood count	£3.46	£3.11	£3.81
	Cost of liver function test	£1.81	£1.63	£1.99
	Cost of kidney function test	£3.46	£3.11	£3.81
	Cost of treatment toxicity monitoring	£3.46	£3.11	£3.81
	Cost of PSA test	£1.81	£1.63	£1.99

Abbreviations: AAP – Abiraterone; CT – Computed tomography; ENZA – Enzalutamide; OLAP – Olaparib; PSA – Prostate specific antigen; TALA – Talazoparib

Since both talazoparib with enzalutamide and olaparib with abiraterone use similar drug monitoring frequency and resource use costs, a change in each of the parameters had [redacted] on the total incremental cost. The parameters with the most impact are presented in **Table 40**.

Table 40: OWSA parameters with the most impact on total incremental cost

Parameter	Lower bound incremental cost	Higher bound incremental cost	Incremental cost difference
Talazoparib with enzalutamide frequency of CT scan (4+ months)	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone frequency of CT scan (4+ months)	[redacted]	[redacted]	[redacted]
Talazoparib with enzalutamide frequency of outpatient visit (consultant led) (4+ months)	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone frequency of outpatient visit (consultant led) (4+ months)	[redacted]	[redacted]	[redacted]

Abbreviations: CT – Computed tomography

B.4.4.2 Scenario analyses

The results of scenario analyses conducted to test the influence of the model assumptions are presented in **Table 41**. Talazoparib with enzalutamide is associated with cost savings compared to olaparib with abiraterone across all examined

scenarios, which aligns with the base case and confirms that talazoparib with enzalutamide is cost-saving under the most plausible assumptions.

Table 41: Scenario analyses results (with PAS for intervention; list price for comparator)

Scenario	Acquisition costs	Resource costs	Misc. costs	Total costs	Incremental costs
Base case					
Talazoparib with enzalutamide	£[redacted]	£40,225	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£40,971	£0	£[redacted]	--
1: Inclusion of AE management costs					
Talazoparib with enzalutamide	£[redacted]	£40,225	£492[a]	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£40,971	£135[a]	£[redacted]	--
2. Inclusion of SRE management costs					
Talazoparib with enzalutamide	£[redacted]	£40,225	£[redacted][b]	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£40,971	£[redacted][b]	£[redacted]	--
3. Inclusion of 3.5% discount rate					
Talazoparib with enzalutamide	£[redacted]	£32,440	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£33,047	£0	£[redacted]	--
4. Inclusion of mid-cycle correction					
Talazoparib with enzalutamide	£[redacted]	£40,482	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£41,232	£0	£[redacted]	--
5A. 20-year time horizon					
Talazoparib with enzalutamide	£[redacted]	£36,445	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£37,124	£0	£[redacted]	--
5B. 10-year time horizon					
Talazoparib with enzalutamide	£[redacted]	£28,636	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£29,175	£0	£[redacted]	--
6A. Generalised gamma for rPFS extrapolation					
Talazoparib with enzalutamide	£[redacted]	£59,534	£0	£[redacted]	[redacted]

Scenario	Acquisition costs	Resource costs	Misc. costs	Total costs	Incremental costs
Olaparib with abiraterone	£[redacted]	£60,625	£0	£[redacted]	--
6B. Log logistic for rPFS extrapolation					
Talazoparib with enzalutamide	£[redacted]	£40,570	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£41,322	£0	£[redacted]	--
6C. Gompertz for rPFS extrapolation					
Talazoparib with enzalutamide	£[redacted]	£64,833	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£66,019	£0	£[redacted]	--
6D. Weibull for rPFS extrapolation					
Talazoparib with enzalutamide	£[redacted]	£29,741	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£30,299	£0	£[redacted]	--
6E. Exponential for rPFS extrapolation					
Talazoparib with enzalutamide	£[redacted]	£30,075	£0	£[redacted]	[redacted]
Olaparib with abiraterone	£[redacted]	£30,640	£0	£[redacted]	

[a] AE costs

[b] SRE costs

Abbreviations: AE – Adverse event; Misc. – Miscellaneous; rPFS – Radiographic progression-free survival; SRE – Skeletal-related event

B.4.5 Subgroup analysis

No subgroup analyses were conducted.

B.4.6 Interpretation and conclusions of economic evidence

A cost comparison analysis was developed for the economic evaluation of talazoparib with enzalutamide versus olaparib with abiraterone. The two combination treatments were assumed to be similar in clinical efficacy and safety, and only costs related to acquisition and monitoring were considered.

The results considered the PAS of talazoparib and list prices for other treatments. Overall, talazoparib with enzalutamide is estimated to generate cost saving to the NHS and PSS of £[redacted] compared to olaparib with abiraterone over the 30-year time horizon.

The deterministic and scenario analyses showed that parameters had very little impact on the overall incremental costs and talazoparib with enzalutamide is consistently associated with cost savings compared to olaparib with abiraterone. It is worth noting that there is an unknown confidential PAS in place for olaparib with abiraterone. However, approximate pricing assessment considering an estimated PAS for olaparib with abiraterone found that talazoparib with enzalutamide remains a cost-neutral treatment option.

To conclude, talazoparib with enzalutamide exhibits a good use of NHS resources and consistently remains a suitable alternative to olaparib with abiraterone whilst providing similar health benefits.

References

1. UK EMC. Talzenna 0.25 mg hard capsules - Summary of Product Characteristics (SmPC). at <https://www.medicines.org.uk/emc/product/10734/smpc/print>
2. NICE. User guide for the cost comparison company evidence submission template. 2022. at <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/cost-comparison-company-evidence-submission-template.docx>
3. NICE. NICE health technology evaluations: the manual. 2023. at <https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741>
4. NICE. Single Technology Appraisal: Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920] Committee Papers. 2023.
5. NICE. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer - Final draft guidance. 2023.
6. Pfizer. NMA Final Technical Report. (Data on file). 2023.
7. Pfizer. Clinical expert validation interview outcomes. (Data on file). 2024.
8. Agarwal N, Zhang T, Efstathiou E, *et al.* The biology behind combining poly [ADP ribose] polymerase and androgen receptor inhibition for metastatic castration-resistant prostate cancer. *Eur J Cancer* 2023. 192: 113249.
9. Murai J, Huang S-YN, Renaud A, *et al.* Stereospecific PARP trapping by BMN 673 and comparison with olaparib and rucaparib. *Mol Cancer Ther* 2014. 13: 433–443.
10. Shen Y, Rehman FL, Feng Y, *et al.* BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. *Clin Cancer Res* 2013. 19: 5003–5015.
11. Zandarashvili L, Langelier M-F, Velagapudi UK, *et al.* Structural basis for allosteric PARP-1 retention on DNA breaks. *Science* 2020. 368: eaax6367.
12. EMC. Xtandi SmPC. 2024. at <https://www.medicines.org.uk/emc/product/10318>
13. Asim M, Tarish F, Zecchini HI, *et al.* Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. *Nat Commun* 2017. 8: 374.
14. Chakraborty G, Armenia J, Mazzu YZ, *et al.* Significance of BRCA2 and RB1 Co-loss in Aggressive Prostate Cancer Progression. *Clin Cancer Res* 2020. 26: 2047–2064.
15. EMA. Talzenna SmPC. 2024. at <https://www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf>

16. EMA. Talzenna EPAR Medicine Overview. 2024. at <https://www.ema.europa.eu/en/documents/overview/talzenna-epar-medicine-overview_en.pdf>
17. MHRA. Talazoparib decision cover letter. 2022. at <https://cms.mhra.gov.uk/system/files/2022-12/mhra-100395-pip01-21.pdf>
18. Sung H, Ferlay J, Siegel RL, *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: 209–249.
19. Cancer Research UK. Prostate cancer statistics. *Cancer Research UK* 2020. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer>
20. NPCA. Annual Report 2021: Results of the NPCA Prospective Audit in England and Wales for men diagnosed from 1 April 2019 to 31 March 2020 and the Impact of COVID-19 in England during 2020. 2022. at <https://www.npca.org.uk/wp-content/uploads/2022/01/NPCA-Annual-Report-2021_Final_13.01.22-1.pdf>
21. NICE. Prostate cancer: diagnosis and management (NG131). *Prostate cancer*
22. NCCN. NCCN Prostate Cancer Guidelines. 2024. at <https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf>
23. Albala DM. Imaging and treatment recommendations in patients with castrate-resistant prostate cancer. *Rev Urol* 2017. 19: 200–202.
24. Parker C, Castro E, Fizazi K, *et al.* Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020. 31: 1119–1134.
25. Shore N, Oliver L, Shui I, *et al.* Systematic Literature Review of the Epidemiology of Advanced Prostate Cancer and Associated Homologous Recombination Repair Gene Alterations. *J Urol* 2021. 205: 977–986.
26. Kirby M, Hirst C & Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. *Int J Clin Pract* 2011. 65: 1180–1192.
27. Francini E, Gray KP, Shaw GK, *et al.* Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry. *Prostate Cancer Prostatic Dis* 2019. 22: 420–427.
28. Chowdhury S, Bjartell A, Lumen N, *et al.* Real-World Outcomes in First-Line Treatment of Metastatic Castration-Resistant Prostate Cancer: The Prostate Cancer Registry. *Target Oncol* 2020. 15: 301–315.
29. Westgeest HM, Kuppen MCP, van den Eertwegh AJM, *et al.* The effects of new life-prolonging drugs for metastatic castration-resistant prostate cancer (mCRPC) patients in a real-world population. *Prostate Cancer Prostatic Dis* 2021. 24: 871–879.
30. Svensson J, Lissbrant IF, Gauffin O, *et al.* Time spent in hormone-sensitive and castration-resistant disease states in men with advanced prostate cancer, and its health economic impact: registry-based study in Sweden. *Scand J Urol* 2021. 55: 1–8.

31. George DJ, Sartor O, Miller K, *et al.* Treatment Patterns and Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer in a Real-world Clinical Practice Setting in the United States. *Clin Genitourin Cancer* 2020. 18: 284–294.
32. Holmstrom S, Naidoo S, Turnbull J, *et al.* Symptoms and Impacts in Metastatic Castration-Resistant Prostate Cancer: Qualitative Findings from Patient and Physician Interviews. *Patient* 2019. 12: 57–67.
33. Boye M, Ribbands A, Leith A, *et al.* Real-world health-related quality of life and caregiver need in patients with metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. *Journal of Clinical Oncology* 2022. 40: 54–54.
34. The burden of symptomatic skeletal events in castrate-resistant prostate cancer patients with bone metastases at three Canadian uro-oncology centres - PubMed. at <https://pubmed.ncbi.nlm.nih.gov/29940132/>
35. Sathiakumar N, Delzell E, Morrisey MA, *et al.* Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999-2006. *Prostate Cancer Prostatic Dis* 2011. 14: 177–183.
36. NICE. Apalutamide with androgen deprivation therapy for treating high-risk hormone-relapsed non-metastatic prostate cancer (TA740). 2021. at <https://www.nice.org.uk/guidance/ta740/resources/apalutamide-with-androgen-deprivation-therapy-for-treating-highrisk-hormonerelapsed-nonmetastatic-prostate-cancer-pdf-82611308252869>
37. NICE. Darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer (TA660). 2020. at <https://www.nice.org.uk/guidance/ta660/resources/darolutamide-with-androgen-deprivation-therapy-for-treating-hormonerelapsed-nonmetastatic-prostate-cancer-pdf-82609252402885>
38. NICE. Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer (TA903). at <June 2023>
39. NICE. Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer. TA741. 2021. at <https://www.nice.org.uk/guidance/ta741/resources/apalutamide-with-androgen-deprivation-therapy-for-treating-hormonesensitive-metastatic-prostate-cancer-pdf-82611309932485>
40. NICE. Enzalutamide for treating hormone-sensitive metastatic prostate cancer (TA712). 2021. at <https://www.nice.org.uk/guidance/ta712/resources/enzalutamide-for-treating-hormonesensitive-metastatic-prostate-cancer-pdf-82611130213573>
41. NICE. Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (TA101). 2006. at <https://www.nice.org.uk/guidance/ta101/resources/docetaxel-for-the-treatment-of-hormonerefractory-metastatic-prostate-cancer-pdf-82598007373765>

42. NICE. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (TA259). 2016. at <https://www.nice.org.uk/guidance/ta259/resources/abiraterone-for-castrationresistant-metastatic-prostate-cancer-previously-treated-with-a-docetaxelcontaining-regimen-pdf-82600499923909>
43. NICE. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316). 2014. at <https://www.nice.org.uk/guidance/ta316/resources/enzalutamide-for-metastatic-hormonerelapsed-prostate-cancer-previously-treated-with-a-docetaxelcontaining-regimen-pdf-82602429802693>
44. NICE. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391). 2016. at <https://www.nice.org.uk/guidance/ta391/resources/cabazitaxel-for-hormonerelapsed-metastatic-prostate-cancer-treated-with-docetaxel-pdf-82602905134021>
45. NICE. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated: © NICE (2016) Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). *BJU International* 2017. 120: 168–184.
46. NICE. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). 2016. at <https://www.nice.org.uk/guidance/ta387/resources/abiraterone-for-treating-metastatic-hormonerelapsed-prostate-cancer-before-chemotherapy-is-indicated-pdf-82602854745541>
47. NICE. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer (TA951). 2024. at <https://www.nice.org.uk/guidance/ta951/resources/olaparib-with-abiraterone-for-untreated-hormonerelapsed-metastatic-prostate-cancer-pdf-82615723963333>
48. NICE. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer (TA887). *prostate cancer* 2023. at <https://www.nice.org.uk/guidance/ta887/resources/olaparib-for-previously-treated-brca-mutationpositive-hormonerelapsed-metastatic-prostate-cancer-pdf-82613738657221>
49. Delon C, Brown KF, Payne NWS, *et al.* Differences in cancer incidence by broad ethnic group in England, 2013–2017. *Br J Cancer* 2022. 126: 1765–1773.
50. Hernández-Alava M & Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. *J Health Econ* 2017. 55: 139–152.
51. Pfizer. TALAPRO 2 CSR. (Data on file). 2022.
52. Agarwal N, Azad AA, Carles J, *et al.* Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2023. 402: 291–303.
53. De Giorgi U, Azad A, Fizazi K, *et al.* Patient-reported outcomes (PROs) with talazoparib (TALA) plus enzalutamide (ENZA) vs. placebo (PBO) plus ENZA in

men with metastatic castration-resistant prostate cancer (mCRPC): Subgroup analysis of patients with novel hormonal therapy (NHT) pretreatment in the TALAPRO-2 study. *J Clin Oncol* 2024. 42:

54. Fizazi K, Shore ND, Fong PCC, *et al.* Patient reported outcomes (PROs) among patients with metastatic castrationresistant prostate cancer (mCRPC) by homologous recombination repair mutations (HRRm) gene clusters: Findings from the phase 3 TALAPRO-2 study cohort 2. *J Clin Oncol* 2024. 42:
55. Fizazi K, Azad AA, Matsubara N, *et al.* First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: the phase 3 TALAPRO-2 trial. *Nat Med* 2024. 30: 257–264.
56. Shore ND, Agarwal N, Azad A, *et al.* Post hoc analysis of rPFS and OS from the TALAPRO-2 (TP-2) study: Genomic subgroups based on likelihood of BRCA or HRR gene alteration status. *JCO* 2024. 42: 136–136.
57. Zschaebitz S, Fizazi K, Matsubara N, *et al.* Exploratory analyses of homologous recombination repair (HRR) gene subgroups and potential associations with secondary efficacy endpoints in the HRR-deficient population from TALAPRO-2. *J Clin Oncol* 2024. 42:
58. Fay A, Fizazi K, Matsubara N, *et al.* 1811P Patient-reported outcomes (PROs) in men with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) mutations receiving talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA: results from a phase III (TALAPRO-2) study. *Annals of oncology* 2023. 34: S980-S981.
59. jones R, De Giorgi U, Zschabitz S, *et al.* Patient-reported pain in men with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) mutations receiving talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA: Results from a phase 3 (TALAPRO-2) study. *Eu Uro Op Sci* 2023. 57: S204–S205.
60. Matsubara N, Fizazi K, Azad AA, *et al.* 1807P Talazoparib (TALA) plus enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC): Subgroup analyses of the all-comers cohort from TALAPRO-2 by homologous recombination repair (HRR) status. *Annals of Oncology* 2023. 34: S977–S978.
61. Zschäbitz S, Agarwal N, Azad AA, *et al.* TALAPRO-2: Phase 3 study of talazoparib + enzalutamide versus placebo + enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer (mCRPC). *Oncol Res Treat* 2023. 46: 113–114.
62. Pfizer. Talazoparib for the First-Line Treatment of Adult Patients with Metastatic Castration-Resistant Prostate Cancer: Network Meta-Analysis. Global NMA Final Technical Report (Data on file). 2023.
63. Pfizer. Feasibility Assessment and Indirect Treatment Comparisons of Talazoparib Versus Key Comparators for Metastatic Castration-Resistant Prostate Cancer in First-Line Setting - Final Technical Report. (Data on file). 2022.

64. Sofia Dias, Nicky J Welton, Alex J Sutton, AE Ades. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2016. at <https://shared-15-24-search.clients.uk.funnelback.com/s/redirect?collection=sheffield-uni-meta&url=https%3A%2F%2Fwww.sheffield.ac.uk%2Fmedia%2F34176%2Fdownload%3Fattachment&auth=pLMQD3EXiHEwZqIw65Vqsg&profile=_default&rank=1&query=TSD2-General-Meta-Analysis-Corrected+%7CincludeFileDownloads%3A%22%24%2B%2B+Yes+%24%2B%2B%22>

65. Turner RM, Jackson D, Wei Y, *et al.* Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. *Statistics in Medicine* 2015. 34: 984–998.

66. R: The R Project for Statistical Computing. at <https://www.r-project.org/>

67. Phillippo DM, Dias S, Ades AE, *et al.* Assessing the performance of population adjustment methods for anchored indirect comparisons: A simulation study. *Statistics in Medicine* 2020. 39: 4885–4911.

68. Carpenter B, Gelman A, Hoffman MD, *et al.* Stan: A Probabilistic Programming Language. *Journal of Statistical Software* 2017. 76: 1–32.

69. Azad A, Fizazi K, Matsubara N, *et al.* Talazoparib (TALA) plus enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC): Safety analyses from the randomized, placebo (PBO)-controlled, phase 3 TALAPRO-2 study. *JCO* 2023. 41: 5053–5053.

70. Agarwal N, Azad A, Carles J, *et al.* LBA17: TALAPRO-2: Phase 3 study of talazoparib (TALA)+ enzalutamide (ENZA) versus placebo (PBO)+ ENZA as first-line (1L) treatment in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *American Society of Clinical Oncology GU* 2023.

71. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, *et al.* LBA16: Final overall survival (OS) in PROpel: Abiraterone (abi) and olaparib (ola) versus abiraterone and placebo (pbo) as first-line (1L) therapy for metastatic castration-resistant prostate cancer (mCRPC). *J Clin Oncol* 2023. doi:10.1200/JCO.2023.41.6_suppl.LBA16

72. EMA. Lynparza SmPC. 2024. at <https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf>

73. EMA. Zytiga SmPC. 2022. at <https://www.ema.europa.eu/en/documents/product-information/zytiga-epar-product-information_en.pdf>

74. Drugs A to Z | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/>

75. Drugs and pharmaceutical electronic market information tool (eMIT). *GOV.UK* 2024. at <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>

76. NHS. National Schedule for NHS costs. 2021. at <https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/>

77. Jones, K., Weatherly, H., Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S., Premji, S., Teo, H. Unit Costs of Health and Social Care 2023. 2023. at <https://kar.kent.ac.uk/105685/1/The%20unit%20costs%20of%20health%20and%20social%20care_Final3.pdf>

78. CPI INDEX 06 : HEALTH 2015=100 - Office for National Statistics. at <https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bz/mm23>

79. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA836). 2022. at <https://www.nice.org.uk/guidance/ta836/documents/committee-papers-2>

80. NICE. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer (TA619). 2022. at <https://www.nice.org.uk/guidance/ta836/documents/committee-papers-2>

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Addendum

Company evidence submission

July 2025

File name	Version	Contains confidential information	Date
ID4004_Talazoparib_ mCRPC_Company submission addendum_11MAR25_[Redacted]	1	No	11th March 2025
ID4004_Talazoparib_ mCRPC_Company submission addendum_ 28JUL25_[Redacted]	2	No	28th July 2025

Contents

Tables and figures

Foreword

This addendum provides an update to the clinical and economic evidence presented in the original company submission (CS) for talazoparib with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated (ID4004).

The original CS presented a cost comparison analysis for talazoparib with enzalutamide versus olaparib with abiraterone. The submission included a Cox-based network meta-analysis (NMA) with a random effects (RE) model to demonstrate clinical similarity in terms of radiographic progression-free survival (rPFS), overall survival (OS), and other clinical outcomes. However, the EAG and NICE appraisal committee Chair concluded that there was insufficient evidence of clinical similarity. The EAG's preferred fixed effects (FE) model for rPFS [redacted] and found talazoparib with enzalutamide [redacted] olaparib with abiraterone. Additionally, the EAG were concerned that the proportional hazards (PH) assumption used in the Cox NMA may not be appropriate and noted that an unanchored matching-adjusted indirect treatment comparison (MAIC) would be more appropriate approach for estimating comparative effectiveness.

As requested by the NICE Associate Director and committee Chair, a fully incremental cost-utility analysis (CUA) versus olaparib with abiraterone has been presented in this addendum. The addendum represents a pragmatic approach to minimise further delays in patient access to treatment, especially considering talazoparib was accepted for use within NHS Scotland for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (SMC2753).[1]

In addition to the CUA, the addendum presents new TALAPRO-2 data from the final prespecified OS analysis (data cutoff date of 3rd September 2024), including a descriptive update of the primary efficacy endpoint blinded independent central review-assessed (BICR) rPFS and safety results. The addendum also presents the results of an unanchored MAIC, which is used in the CUA to model treatment arms independently, thereby addressing the EAG's concerns with PH in the Cox NMA in the original CS.

Consistent with the decision problem and final scope addressed in the original CS, the company is seeking the same positioning and recommendation as olaparib with abiraterone in TA951. Talazoparib and olaparib are in the same drug class of poly adenosine diphosphate ribose polymerase (PARP) inhibitors. PARP inhibitors prevent DNA repair, leading to the accumulation of DNA damage and cell death through synthetic lethality. Similarly, enzalutamide and abiraterone are both new hormonal agents (NHAs) that inhibit the androgen receptor pathway. The marketing authorisations of each combination are comparable, and UK clinical experts consulted in August 2024 for the original CS confirmed that talazoparib with enzalutamide is expected to be used in the same population as olaparib with abiraterone.[2]

Executive summary

Clinical effectiveness (addendum to Document B, Section B.2 and B.3):

- In the final prespecified OS analysis of TALAPRO-2 (cutoff date of 3rd September 2024), talazoparib with enzalutamide demonstrated a statistically significant improvement in OS compared to placebo with enzalutamide.[3] This represents an improvement compared with the primary analysis (cutoff date of 16th August 2022) presented in the original CS, which showed a numerical but not statistically significant benefit (see **Section 1.1.2**).[4]
    - A hazard ratio (HR) of 0.796 (95% CI: 0.661, 0.958 2-sided p=0.0155) was observed in favour of the talazoparib with enzalutamide arm.[3]
    - The median OS was 45.8 months (95% CI: 39.4, 50.8) in the talazoparib with enzalutamide arm and 37.0 months (95% CI: 34.1, 40.4) in the placebo with enzalutamide arm.[3] The probability of survival at 48 months was 48.5% (95% CI: 43.3%, 53.5%) and 38.4% (95% CI: 33.4%, 43.4%) for the talazoparib with enzalutamide and placebo with enzalutamide arms, respectively.[3]
- In the descriptive update for rPFS, talazoparib with enzalutamide demonstrated a statistically significant improvement compared to placebo with enzalutamide (see **Section 1.1.3**).[3]
    - A HR of 0.667 (95% CI: 0.551, 0.807; 2-sided p<0.0001) was observed in favour of the talazoparib with enzalutamide arm.[3]
    - The median BICR-assessed rPFS was 33.1 months (95% CI: 27.4, 39.0) in the talazoparib with enzalutamide arm and 19.5 months (95% CI: 16.6, 24.7) in the placebo with enzalutamide arm.[3]
    - These results, in alignment with the conclusions in the original CS, highlight the clinical efficacy of talazoparib with enzalutamide for treating mCRPC.
- As per the original CS, the safety profile of talazoparib with enzalutamide was consistent with the known safety profiles of each agent used as monotherapy with no new safety signals identified in the latest data cutoff (see Section 1.3).[3]

- Results from the MAIC primary analysis (which adjusted for stratification factors and prognostic factors) suggest that talazoparib with enzalutamide is associated with [redacted] (see **Section 1.2**).

Cost-effectiveness (addendum to Document B, Section B.4):

- When applying a patient access scheme (PAS) discount of [redacted] to talazoparib, the deterministic base case results show that talazoparib with enzalutamide is associated with [redacted] incremental quality-adjusted life years (QALYs) at an incremental cost of [redacted], which translates to a [redacted] incremental cost-effectiveness ratio (ICER) compared to olaparib with abiraterone over a 30-year time horizon, and a net monetary benefit of [redacted] (see **Section 2.7**).
- Based on the probabilistic sensitivity analysis (PSA), treatment with talazoparib with enzalutamide in patients with mCRPC was associated with incremental costs and QALYs of [redacted] and [redacted], respectively, with a corresponding [redacted] ICER compared to olaparib with abiraterone, and a net monetary benefit of [redacted]. The mean probabilistic results [redacted] to the deterministic results, indicating that the model is robust to parameter uncertainty (see **Section 2.8**).
- The parameters with the biggest impact on the ICER are [redacted]
- Scenario analyses were performed to test underlying model assumptions and the use of alternative input parameters. [redacted] (see **Section 2.8**).

- We acknowledge the cost-effectiveness results presented in this addendum do not consider commercially confidential PAS discounts for olaparib, enzalutamide and subsequent treatments, however, we believe both the deterministic and probabilistic base case ICERs for talazoparib with

enzalutamide [redacted] cost-effective compared to olaparib with abiraterone when PAS discounts are applied.

1 Clinical effectiveness (addendum to Document B, Section B.2 and B.3)

1.1 *Clinical effectiveness results of the relevant studies*

1.1.1 Summary of primary analysis results

As per the original CS, TALAPRO-2 represents the primary source of clinical effectiveness evidence for talazoparib with enzalutamide in mCRPC. Data presented in the original CS were from the primary analysis of Part 2, Cohort 1, with a data cutoff date of 16th August 2022, which represented the final analysis for the primary outcome (BICR-assessed rPFS) and interim analyses for the secondary outcomes (including OS).[4,5]

As presented in the original CS, at the 16th August 2022 data cutoff date, talazoparib with enzalutamide met the primary endpoint demonstrating a statistically significant improvement in BICR-assessed rPFS compared with placebo with enzalutamide, with an observed hazard ratio (HR) of 0.63 (95% confidence interval [CI]: 0.51, 0.78; p<0.0001).[4,5] Although the OS data were immature at the time of submission, talazoparib with enzalutamide was associated with a numerically lower overall risk of death, with an HR of 0.888 (95% CI: 0.693, 1.138; 2-sided p=0.3472), and a higher probability of being event-free at 12, 24, and 36 months.[4,5] The rPFS and OS data from this analysis are presented in **Section B.3.6.1** and **Section B.3.6.3** of Document B of the original CS, respectively.

Since the original CS, the final prespecified OS analysis has been conducted, with a cutoff date of 3rd September 2024. This includes a descriptive update of rPFS and safety outcomes.

1.1.2 Descriptive update for primary efficacy endpoint: rPFS by BICR

The BICR-assessed rPFS results for the Cohort 1 Part 2 all-comers ITT population from the descriptive update (median follow up: 47.0 months for the talazoparib with enzalutamide arm and 46.9 months for the placebo with enzalutamide arm) are consistent with the previous data cut (cutoff date of 16th August 2022).[3] As presented

in **Table 1** and **Figure 1**, talazoparib with enzalutamide maintained a statistically significant and clinically meaningful improvement in BICR-assessed rPFS compared to placebo with enzalutamide, with an observed HR of 0.667 (95% CI: 0.551, 0.807; 2-sided p<0.0001) in favour of the talazoparib with enzalutamide arm.[3] The median BICR-assessed rPFS was 33.1 months (95% CI: 27.4, 39.0) in the talazoparib with enzalutamide arm and 19.5 months (95% CI: 16.6, 24.7) in the placebo with enzalutamide arm.[3]

Table 1: TALAPRO-2: Summary of BICR-assessed rPFS for the Cohort 1 Part 2 all-comers ITT population at final data cutoff 3rd September 2024 (N=805)

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median rPFS by BICR, months (95% CI)[a]	33.1 (27.4, 39.0)	19.5 (16.6, 24.7)	0.667 (0.551, 0.807)	<0.0001
Events (%)	202 (50.2)	231 (57.3)	--	--
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	--	--
24 months	[redacted]	[redacted]	--	--
36 months	[redacted]	[redacted]	--	--
48 months	[redacted]	[redacted]	--	--

[a] Based on the Brookmeyer-Crowley method.
[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.
Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; ITT – Intention-to-treat; rPFS – Radiographic progression-free survival
Source: TALAPRO-2 1.0 Interim All-comers CSR – Table 15.[3]

Figure 1: Kaplan-Meier plot of BICR-assessed rPFS for the Cohort 1 Part 2 all-comers ITT population at final data cutoff 3rd September 2024 (N=805)

Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; ITT – Intention-to-treat; rPFS – Radiographic progression-free survival

Source: TALAPRO-2 1.0 Interim All-comers CSR – Figure 3.[3]

1.1.3 Key secondary efficacy endpoint: OS

As presented in **Table 2** and **Figure 2,** results from the final prespecified analysis (median follow up: 52.5 months for the talazoparib with enzalutamide arm and 53.0 months for the placebo with enzalutamide arm) confirms that talazoparib with enzalutamide was associated with a statistically significant and clinically meaningful improvement in OS compared to placebo with enzalutamide, with an observed HR of 0.796 (95% CI: 0.661, 0.958 2-sided p=0.0155) in favour of the talazoparib with enzalutamide arm.[3] The median OS was 45.8 months (95% CI: 39.4, 50.8) in the talazoparib with enzalutamide arm and 37.0 months (95% CI: 34.1, 40.4) in the placebo with enzalutamide arm.[3] The probability of survival at 48 months was [redacted] and [redacted] for the talazoparib with enzalutamide and placebo with enzalutamide arms, respectively.[3]

Table 2: Summary of OS for the Cohort 1 Part 2 all-comers ITT population at the final data cutoff of 3rd September 2024 (N=805)

	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median[a] (95% CI), months	45.8 (39.4, 50.8)	37.0 (34.1, 40.4)	0.796 (0.661, 0.958)	0.0155
Number of events n(%)	211 (52.5%)	243 (60.3)	-	-
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	-	-
24 months	[redacted]	[redacted]	-	-
36 months	[redacted]	[redacted]	-	-
48 months	[redacted]	[redacted]	-	-
60 months	[redacted]	[redacted]	-	-

[a] Based on the Brookmeyer-Crowley method.
[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.
Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; OS – Overall Survival
Source: TALAPRO-2 1.0 Interim All-comers CSR – Table 18.[3]

Figure 2: Kaplan-Meier plot of OS for the Cohort 1 Part 2 all-comers ITT population at the final data cutoff of 3rd September 2024 (N=805)

Abbreviations: CI – Confidence interval; HR – Hazard ratio; ITT – Intention-to-treat; OS – Overall survival
Source: TALAPRO-2 1.0 Interim All-comers CSR – Figure 5.[3]

1.2 *Indirect and mixed treatment comparisons*

1.2.1 MAIC

As noted in the **Foreword**, an unanchored MAIC was conducted to estimate the comparative efficacy of talazoparib with enzalutamide and olaparib with abiraterone for mCRPC.

1.2.1.1 Identification of relevant studies

The MAIC was conducted in January 2025 based on data from a clinical SLR from 8 August 2024, which identified 49 unique studies, of which 42 had published results and 7 were ongoing with no published results.[6] For more information on this SLR, please refer to the technical report provided as part of the PDF reference pack (please note that this SLR is different to the one presented in the original CS).

As expected, the pivotal trials for the intervention and sole comparator of interest were TALAPRO-2 (talazoparib with enzalutamide) and PROpel (olaparib with abiraterone) as per **Section B.3.9.1** in the original CS. A feasibility assessment was therefore undertaken using these trials to determine the suitability of an unanchored MAIC to indirectly compare talazoparib with enzalutamide and olaparib with abiraterone and to determine the presence of heterogeneity in terms of trial design characteristics, patient eligibility criteria, baseline patient characteristics, outcome characteristics (i.e., definitions and methods of reporting outcomes).[7] Although the feasibility assessment reported some inter-trial heterogeneity, these differences did not preclude analyses. Since no common comparators exist between the TALAPRO-2 and PROpel studies, unanchored MAICs were performed for rPFS and OS.

1.2.1.2 Methodology

MAICs were conducted by using individual patient data (IPD) from TALAPRO-2 (data cutoff date 3rd September 2024) to match patients to summary-level data from PROpel based on eligibility criteria and then adjusting for prognostic factors and treatment effect modifiers.[8,9] All analyses were conducted using R (version 3.6.1) based on the methods developed by Signorovitch et al.[10] and as implemented by the NICE Evidence Synthesis

Technical Support Document (TSD) Series.[11] The following sections describe the MAIC methods in more detail.

Matching based on eligibility criteria

Eligibility criteria were mostly similar between TALAPRO-2 and PROpel except for Brief Pain Inventory - Short Form (BPI-SF) eligibility. PROpel had no eligibility restrictions based on pain as per the BPI-SF, while TALAPRO-2 required patients to have a score ≤3 on question 3 of the BPI-SF (worst pain in the last 24 hours). Since PROpel was broader than TALAPRO-2 for BPI-SF, and otherwise the trials were sufficiently similar, matching was not necessary and therefore no matching was performed.

Adjusting for prognostic factors

Key factors for adjustment were identified and ranked in order of importance based on published analyses on prognostic strength in mCRPC,[12] and refined based on clinical expert opinion. The final list of 12 factors, ranked from one (most important) to 12 (least important), with availability in TALAPRO-2 IPD and PROpel is presented in **Table 3**.

The analysis adjusted for all prognostic factors available in both trials, except for BPI-SF (as noted above), time to mCRPC from continuous androgen deprivation therapy (ADT; not reported in either trial), and neutrophil to lymphocyte ratio (not reported in PROpel). Scenario analyses were conducted adjusting incrementally for each factor in order of importance. Although not originally ranked, presence of BRCA1, BRCA2, or PALB2 HRR gene alterations were also considered based on external clinical input, so exploratory analyses were conducted for BRCA1 and BRCA2, but not PALB2 HRR gene alterations as it was not reported in PROpel.

Table 3: Adjustment of prognostic factors for PROpel

Rank	Identified Factor	Available for TALAPRO-2	Available for PROpel	Adjusted variable
1	Time to mCRPC from continuous ADT	No [a]	No [a]	No
2	Presence of liver metastases	Yes	Yes	Yes
3	Number of bone metastases (<10 vs >10)	Yes [b]	Yes [b]	Yes
4	ECOG (0-1 vs 2, 3)	Yes [c]	Yes [c]	Yes
5	BPI-SF	Yes	Yes	No
6	PSA kinetics or PSA levels in absence of kinetics data	Yes	Yes	Yes
7	Gleason score	Yes	Yes	Yes
8	Haemoglobin level	Yes	Yes	Yes
9	Lactate dehydrogenase level	Yes	Yes	Yes
10	Albumin level	Yes	Yes	Yes
11	Alkaline phosphatase level	Yes	Yes	Yes
12	Neutrophil to lymphocyte ratio	Yes [d]	No	No
Exploratory*	BRCA1	Yes	Yes	Yes
Exploratory*	BRCA2	Yes	Yes	Yes
Exploratory*	PALB2	Yes	No	No

[a] Trial reports median time from initial diagnosis to randomisation date.
[b] Trial reports presence/absence of bone metastases.
[c] All patients have ECOG 0 or 1.
[d] Calculated from number of neutrophils and lymphocytes.
Abbreviations: ADT = androgen deprivation therapy; BPI-SF = Brief Pain Index - Short Form; ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen

After completing the matching phase, patients remaining from TALAPRO-2 were weighted using a logistic regression, $\log(w_{it}) = \alpha_0 + \boldsymbol{\alpha}_1^T \boldsymbol{X}_{it}$, where $\boldsymbol{X}_{it}$ is the covariate vector for the ith individual receiving treatment t; and where the regression parameters, $\boldsymbol{\alpha_1}$, are estimated by a method-of-moments. Method-of-moments is typically chosen both due to only having summary-level data for comparator trials and because it guarantees a close balancing of covariates between comparison trials of interest. That is, after reweighting patients, the means (or proportions) and standard deviations of covariates from TALAPRO-2 should be almost exactly equal to those published in the comparator study.[13,14]

Adjusting for stratification factors

Patients in TALAPRO-2 were stratified at randomisation by HRR alteration status and prior NHT or taxane-based therapy in the CSPC stage (yes/no), so these factors were also adjusted for in the MAIC. PROpel reported prior hormonal therapy and prior taxane-based therapy per Interactive Web Response System (IWRS) as separate variables, while TALAPRO-2 IPD reported these variables per electronic data capture (EDC) separately but a combined variable per IWRS. To allow for adjustment of prior therapy stratification factors, the separated variables per EDC (rather than IWRS) were used. The proportion of patients with stratification factors per EDC versus IWRS were very similar; therefore, using EDC stratification values was considered appropriate.

Estimating indirect relative treatment effects

Following the population adjustment of TALAPRO-2 to PROpel, estimates of the comparative efficacy of talazoparib with enzalutamide versus olaparib with abiraterone were derived as the difference between (a) an estimate of the outcome of interest for patients in the comparator study, had they received talazoparib with enzalutamide, and (b) the estimated outcome based on published summary-level data from PROpel.

For rPFS and OS, pseudo-IPD representing the patients in PROpel were derived by digitising published Kaplan Meier (KM) curves and applying the Guyot method.[15] A dataset combining weighted IPD and pseudo-IPD (setting weights for pseudo-observations equal to 1) was then used to fit a weighted Cox proportional hazards model with a binary treatment indicator (i.e., for talazoparib with enzalutamide versus the comparator treatment). The estimated regression coefficient for the treatment indicator was used to represent the log HR for talazoparib with enzalutamide versus the comparator treatment, and the corresponding variance was estimated using a robust sandwich estimator. Effect estimates were exponentiated and reported as HRs with 95% CIs.

MAIC performance assessment and scenario analysis

The effective sample size (ESS) was calculated to reflect the sample size of the weighted population; as calculated by $ESS = (\sum w_i)^2/(\sum w_i^2)$, where w_i, $i = 1, \ldots N$, are the patient

weights. A low ESS compared to the original sample size N indicates large differences in patient weights due to large imbalances in patient populations prior to reweighting.[13] Note that concrete guidance on ESS is not currently available, although an ESS of >43% of the original sample size is occasionally cited as a NICE guideline for sufficient ESS[16].

Population differences between TALAPRO-2 and PROpel were assessed using standardised mean differences (SMDs), where an SMD between 0 and 0.1 was considered a small difference, an SMD >0.1 and ≤0.2 was a moderate difference, and an SMD of >0.2 was a substantial difference.[17]

Scenario analyses were conducted to investigate the impact on the treatment effect estimates, ESS, and SMD when adjusting for additional covariates in the analyses. These analyses were conducted sequentially, adjusting incrementally for the remaining factors in order of importance, until the final model contained all available factors.

1.2.1.3 Results

Table 4 presents the distribution of baseline characteristics before and after the adjusting process. After adjustment, the patient characteristics of TALAPRO-2 matched those of PROpel.

Table 4: Unadjusted and adjusted baseline characteristics

aracteristics	PROpel	TALAPRO-2														
		Naïve	1 Strat Factor	2 Strat Factors	3 Strat Factors	1 Factor	2 Factors	3 Factors	4 Factors	5 Factors	6 Factors	7 Factors	8 Factors	9 Factors (Primary)	10 Factors (Exploratory)	11 Factc (Explorat
R alt. status (%)	27.8%	[redacted]	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%
or NHT (%)	0.3%	[redacted]	[redacted]	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
ior Taxane (%)	24.3%	[redacted]	[redacted]	[redacted]	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%
Liver tastases (%)	3.8%	[redacted]	[redacted]	[redacted]	[redacted]	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%
Bone tastases (%)	87.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%
OG = 1 (%)	28.1%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%
SA [a] > 17.9 µg/L (%)	50.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
eason score ≥ 8 (%)	66.4%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66.4%	66.4%	66.4%	66.4%	66.4%	66.4%	66.4%
GB [b] (mean [SD])	130.5 (12.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)	130.5 (12
H [b,c] (mean [SD])	3.9 (1.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.9 (1.3)	3.9 (1.3)	3.9 (1.3)	3.9 (1.3)	3.9 (1.3
Albuminb ean [SD])	42.4 (3.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42.4 (3.9)	42.4 (3.9)	42.4 (3.9)	42.4 (3.
LP [b] (mean [SD])	2.6 (2.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.6 (2.1)	2.6 (2.1)	2.6 (2.1
RCA1 (%)	2.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.3%	2.3%
RCA2 (%)	9.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.5%
N or ESS	*N = 399*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*ESS = 2*
Mean SMD		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*0.000*

[a] PSA level was converted to a dichotomous variable and used the median PSA level from PROpel as the cut-off (17.9 µg/L). To achieve half of the population with PSA levels below the median and half with PSA levels above median, the sample size of PROpel was set to 398 patients for this variable. Grey shading denotes when the value for that characteristic (i.e., row) has been adjusted from the PROpel value.
[b] The mean and standard deviation were estimated from the reported median and range using the estmeansd package in R.
[c] PROpel reported in µkat/L whereas TALAPRO-2 used U/L. A conversion of 1 µkat/L = 60 U/L was performed to match the unit used in PROpel
Abbreviations: ALP = alkaline phosphatase level; BPI-SF = Brief Pain Inventory - Short Form; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; HGB = haemoglobin level; HRR = homologous recombination repair; LDH = lactate dehydrogenase level; MAIC = matching-adjusted indirect comparison; NHT = novel hormonal therapy; PSA = prostate specific antigen; SD = standard deviation; SMD = standardised mean difference

rPFS

The naïve comparison of rPFS for patients treated with talazoparib with enzalutamide versus olaparib with abiraterone produced a HR of [redacted]. In the primary MAIC analysis (all factors adjusted for), the result was [redacted]. The direction of results was [redacted] (i.e., analyses that adjust for each new factor incrementally). Exploratory analyses adjusting for BRCA gene alterations [redacted] to the primary analysis. The results for rPFS comparing TALAPRO-2 vs PROpel before and after adjustment are presented in **Figure 3**. Weighted KM results, after adjusting for all available factors for the primary MAIC analysis, are presented in **Figure 4.**

Figure 3: Summary of rPFS results for TALPRO-2 vs PROpel

Note: An HR below 1.0 indicates an improved outcome for TALA+ENZA relative to OLAP+AAP.
Abbreviations: ALP = alkaline phosphatase level; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; HGB = haemoglobin level; HR = hazard ratio; HRR= homologous recombination repair; LDH = lactate dehydrogenase level; NHT = novel hormonal therapy; OLAP+AAP = olaparib plus abiraterone acetate; PSA = prostate specific antigen; rPFS = radiographic progression-free survival; SMD = standardised mean difference; TALA+ENZA = talazoparib with enzalutamide.

Figure 4: Weighted rPFS KM for TALAPRO-2 vs PROpel (primary analysis)

Abbreviations: CI = confidence interval; KM = Kaplan-Meier; OLAP+AAP = olaparib with abiraterone acetate; rPFS = radiographic progression-free survival; TALA+ENZA = talazoparib with enzalutamide

OS

The naïve comparison of OS for patients treated with talazoparib with enzalutamide versus olaparib with abiraterone produced a HR of [redacted]. In the primary MAIC analysis (all factors adjusted for), the result was [redacted]. The direction of results was [redacted] with the primary analyses for all scenario analyses. Exploratory analyses adjusting for BRCA gene alterations produced [redacted] result to the primary analysis. The results for OS comparing TALAPRO-2 versus PROpel before and after adjustment are presented in **Figure 5**. Weighted KM results after adjusting for all available factors for the primary MAIC analysis are presented in **Figure 6**.

Figure 5: Summary of OS results for TALAPRO-2 vs PROpel

Note: An HR below 1.0 indicates an improved outcome for TALA+ENZA relative to OLAP+AAP.
Abbreviations: ALP = alkaline phosphatase level; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; HGB = haemoglobin level; HR = hazard ratio; HRR = homologous recombination repair; LDH = lactate dehydrogenase level; NHT = novel hormonal therapy; OLAP+AAP = olaparib plus abiraterone acetate; OS = overall survival; PSA = prostate specific antigen; SMD = standardised mean difference; TALA+ENZA = talazoparib with enzalutamide.

Figure 6: Weighted OS KM vs TALAPRO-2 vs PROpel (primary analysis)

Abbreviations: CI = confidence interval; KM = Kaplan-Meier; OLAP+AAP = olaparib plus abiraterone acetate; OS = overall survival; TALA+ENZA = talazoparib with enzalutamide

1.3 *Adverse reactions*

As per the original CS (see **Section B.3.10** of Document B), the primary analysis (data cutoff date of 16th August 2022) showed an adverse event (AE) profile of talazoparib with enzalutamide that was consistent with the known safety profiles of each agent used as monotherapy.

1.3.1 Extent of exposure

In the final prespecified OS analysis (cutoff date of 3rd September 2024), the median duration of talazoparib treatment (in the talazoparib with enzalutamide arm) was [redacted], with a median relative dose intensity (RDI) of [redacted]; this was [redacted] than the median duration of placebo treatment (in the placebo with enzalutamide arm) at [redacted]. A summary of exposure to the study drugs for the Cohort 1 Part 2 all-comers safety population is presented in **Table 5**.

The median duration of enzalutamide treatment was [redacted] in the talazoparib arm compared with the placebo arm at [redacted], respectively (median relative dose intensity: [redacted]).[4] A summary of exposure to enzalutamide is presented in

Table 6.

Table 5: TALAPRO-2: Summary of talazoparib/placebo dosing exposure for the Cohort 1 Part 2 all-comers safety population at final data cutoff 3rd September 2024 (N=799)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)	Total (n=799)
Duration of treatment,[a] weeks			
N			
Mean (SD)			
Median (range)			
Relative dose intensity[b] (%)			
Mean (SD)			
Median (range)			
Dose interruptions, n (%)			
Due to AE			
Due to other reasons			
Dose reductions, n (%)			
Due to AE			
Due to other reasons			

[a] Treatment duration (weeks) is defined as (date of last dose – date of first dose +1)/7.
[b] Relative dose intensity (%) is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in %.
Abbreviations: AE – Adverse event; SD – Standard deviation
Source: TALAPRO-2 1.0 Interim All-comers CSR - Table 13[3]

Table 6: TALAPRO-2: Summary of enzalutamide dosing exposure for the Cohort 1 Part 2 all-comers safety population at final data cutoff 3rd September 2024 (N=799)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)	Total (n=799)
Duration of treatment,[a] weeks			
N			
Mean (SD)			
Median (range)			
Relative dose intensity[b] (%)			
Mean (SD)			
Median (range)			
Dose interruptions, n (%)			
Due to AE			
Due to other reasons			
Dose reductions, n (%)			
Due to AE			
Due to other reasons			

[a] Treatment duration (weeks) is defined as (date of last dose – date of first dose +1)/7.
[b] Relative dose intensity (%) is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in %.
Abbreviations: AE – Adverse event; SD – Standard deviation
Source: TALAPRO-2 1.0 Interim All-comers CSR - Table 14[3]

1.3.2 Overview of adverse events

As presented in the original CS, at the primary analysis (16th August 2022 data cut-off date), the rate of treatment-emergent adverse events (TEAEs) was similar for the talazoparib and placebo arms (98% vs 95%).[4,5] The most common all-cause AEs of any grade in the talazoparib arm (≥30% of patients) were anaemia, neutropenia, and fatigue,[4] and the most common grade ≥3 AEs (≥10% of patients) in the talazoparib arm were anaemia (46%) and neutropenia (18%).[4,5] SAEs were reported more frequently for participants in the talazoparib with enzalutamide treatment arm than for participants in the placebo with enzalutamide treatment arm.[4]

Updated safety results from the final OS analysis (data cutoff date of 3rd September 2024) were generally consistent with the primary analysis.[3] The rate of TEAEs remained similar between talazoparib with enzalutamide and placebo with enzalutamide arms (99% vs 96%, respectively).[3] Grade 5 AEs were reported at a similar frequency (3.5% vs 5.0%, respectively), while grade 3 or 4 AEs were reported more frequently in the talazoparib with enzalutamide arm (76% vs 45%, respectively).[3] SAEs were reported more frequently in the talazoparib with enzalutamide arm (45.7%)

than the placebo with enzalutamide arm (31.4%).[3] **Table 7** presents an updated summary of the TEAEs observed in TALAPRO-2.

As noted in the original CS (see **Section B.3.10** of Document B), in the TALAPRO-2 study, there was a notable occurrence of anaemia. According to the trial protocol, talazoparib dose reduction or interruption was not mandated unless anaemia reached grade 3 or higher. Additionally, significant proportion of participants already had grade 1-2 anaemia at the start of the trial.

UK clinical experts consulted by the company stated that they would likely manage anaemia more proactively in clinical practice than was allowed in TALAPRO-2. In practice, patients would be closely monitored to allow for early intervention upon identifying signs or symptoms of anaemia. This approach aims to minimise the severity of anaemia and reduce the need for transfusions. Monitoring blood counts diligently during the initial 3-4 months of treatment, when the risk of anaemia is highest, could facilitate this process. Although anaemia is recognised as the most common treatment-related adverse event (TRAE), UK clinical experts believe that its burden in real-life practice will not parallel that observed in the TALAPRO-2. They contend that anaemia is predominantly manageable on an outpatient basis. UK clinical experts also stated that anaemia from the use of PARP inhibitor + new hormonal agent (NHA) combination is expected and easily detectable in practice.

Table 7: Summary of TEAEs for the Cohort 1 Part 2 all-comers safety population at final data cutoff 3rd September 2024 (N=799)

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any TEAE (%)	394 (99.0)	316 (79.4)	384 (95.8)	199 (49.6)
Serious TEAE (%)	182 (45.7)	-	126 (31.4)	-
Grade 5 TEAE (%)	14 (3.5)	-	20 (5.0)	-
Discontinued from study due to TEAE (%)[a]	14 (3.5)	-	20 (5.0)	-
TEAE resulting in drug discontinuation (%)				
Talazoparib or placebo	86 (21.6)	-	52 (13.0)	-
Enzalutamide	53 (13.3)	-	48 (12.0)	-
TEAE resulting in dose reduction (%)				
Talazoparib or placebo	217 (54.5)	-	29 (7.2)	-
Enzalutamide	61 (15.3)	-	33 (8.2)	-
TEAE resulting in dose interruption (%)				

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Talazoparib or placebo	260 (65.3)	-	99 (24.7)	-
Enzalutamide	175 (44.0)	-	91 (22.7)	-
Most common all grade AE (in ≥10% of patients) (%)				
Anaemia	270 (67.8)	195 (49.0)	80 (20.0)	18 (4.5)
Neutrophil count decreased	150 (37.7)	77 (19.3)	29 (7.2)	6 (1.5)
Fatigue	139 (34.9)	17 (4.3)	121 (30.2)	8 (2.0)
Back pain	107 (26.9)	13 (3.3)	83 (20.7)	4 (1.0)
Platelet count decreased	102 (25.6)	29 (7.3)	16 (4.0)	4 (1.0)
White blood cell count decreased	96 (24.1)	27 (6.8)	19 (4.7)	0
Decreased appetite	89 (22.4)	6 (1.5)	67 (16.7)	4 (1.0)
Fall	89 (22.4)	11 (2.8)	68 (17.0)	8 (2.0)
Nausea	85 (21.4)	2 (0.5)	53 (13.2)	3 (0.7)
Constipation	78 (19.6)	1 (0.3)	73 (18.2)	2 (0.5)
Arthralgia	69 (17.3)	2 (0.5)	87 (21.7)	2 (0.5)
Diarrhoea	63 (15.8)	1 (0.3)	60 (15.0)	1 (0.2)
Asthenia	61 (15.3)	12 (3.0)	38 (9.5)	4 (1.0)
Hypertension	61 (15.3)	25 (6.3)	68 (17.0)	33 (8.2)
Dizziness	55 (13.8)	4 (1.0)	25 (6.2)	2 (0.5)
Weight decreased	53 (13.3)	4 (1.0)	43 (10.7)	3 (0.7)
Hot flush	51 (12.8)	0	56 (14.0)	0
Lymphocyte count decreased	51 (12.8)	25 (6.3)	23 (5.7)	4 (1.0)
Oedema peripheral	47 (11.8)	0	27 (6.7)	0
Dyspnoea	45 (11.3)	2 (0.5)	25 (6.2)	2 (0.5)
Pain in extremity	43 (10.8)	1 (0.3)	35 (8.7)	1 (0.2)
Headache	40 (10.1)	1 (0.3)	39 (9.7)	1 (0.2)

The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.
Participants are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
a) Participants who have an AE record that indicates that the AE caused the Participants to be discontinued from the study.
The denominator to calculate percentages is N, the number of participants in the safety analysis set within each treatment group. Participants reporting more than one AE within a preferred term are counted only once in that preferred term. For participants reporting more than one AE within a system organ class or preferred term, the AE with maximum grade is included in the table.
Abbreviations: TEAE – Treatment-emergent adverse event
Source: TALAPRO-2 1.0 Interim All-comers CSR – Table 32, Table 33, Table 14.3.1.1.11.[3]

Skeletal-related events (SREs) were reported [redacted] for participants in the talazoparib with enzalutamide treatment arm than for participants in the placebo with enzalutamide treatment arm.[3] [redacted], observed in [redacted] and [redacted] of participants in the talazoparib with enzalutamide arm and placebo with enzalutamide arm, respectively.[3] **Table 8** reports the SREs in the Cohort 1 Part 2 all-comers safety population.

Table 8: Summary of SREs for the Cohort 1 Part 2 all-comers safety population at final data cutoff 3rd September 2024 (N=799)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)
Any SRE (%)	[redacted]	[redacted]
Non-symptomatic fracture (%)	[redacted]	[redacted]
Radiotherapy to bone (%)	[redacted]	[redacted]
Spinal cord compression (%)	[redacted]	[redacted]
Surgery to bone (%)	[redacted]	[redacted]
Symptomatic fracture (%)	[redacted]	[redacted]

Participants are only counted once per treatment event. MedDRA v25 coding dictionary applied.

Abbreviations: SRE – Skeletal related event

Source: TALAPRO-2 1.0 Interim All-comers CSR - Table 44[3]

1.4 *Interpretation of clinical effectiveness and safety evidence*

As described in **Section 1.1.3**, the final prespecified OS analysis of TALAPRO-2 shows that talazoparib with enzalutamide is associated with a statistically significant improvement in OS compared with placebo with enzalutamide.[3] This represents an improvement compared with the data cut in the original CS (detailed in **Table 12; Section B.3.6.3, Document B**), which showed a numerical but not statistically significant benefit.[4] In terms of rPFS, the descriptive update in the final analysis showed that talazoparib with enzalutamide is associated with a statistically significant improvement compared to placebo with enzalutamide.[3] These results, in alignment with the conclusions in the original CS, demonstrate the clinical efficacy of talazoparib with enzalutamide for treating mCRPC.

As per the original CS (see **Section B.3.10** of Document B), the safety profile of talazoparib with enzalutamide was consistent with the known safety profiles of each agent used as monotherapy with no new safety signals identified in the latest data cut (see **Section 1.3**).[3]

Results from the MAIC primary analysis (which adjusted for stratification factors and all prognostic factors available in both trials except for BPI-SF) suggest that talazoparib with enzalutamide is associated with statistically significant improvements in rPFS and numerical improvements in OS compared with olaparib with abiraterone.

2 Cost-effectiveness (addendum to Document B, Section B.4)

2.1 *Economic analysis*

As requested by the Associate Director and the NICE committee Chair, a fully incremental CUA of talazoparib with enzalutamide versus olaparib with abiraterone was developed for patients with mCRPC for whom chemotherapy is not clinically indicated. An overview of the model is provided in **Table 9.**

Table 9: Overview of the economic model

Factor	Details	Rationale
Population	Adult patients with mCRPC in whom chemotherapy is not clinically indicated	In line with NICE scope and licensed indication
Intervention	Talazoparib with enzalutamide	In line with scope
Comparators	Olaparib with abiraterone (and prednisone or prednisolone)	In line with scope
Perspective on costs	NHS and PSS in England and Wales	In line with NICE reference case[18]
Perspective on outcomes	All health effects for patients	In line with NICE reference case[18]
Type of economic evaluation	CUA	In line with EAG and NICE committee preference
Model type	A three health-state partitioned survival model (rPFS, PD, and death)	Consistent with TA951 and other recent appraisals in prostate cancer (TA580, TA660, TA712, TA740, TA741)[19–24]
Time horizon	Lifetime horizon (set at 30 years in the base case)	Sufficient to capture all important differences in costs and outcomes in line with NICE reference case,[18] and consistent with TA951[19]
Cycle length	1 month (30.44 days) with half-cycle correction	Sufficient granularity to capture costs and effects, and consistent with TA951[19]
Discounting	3.5% for both costs and outcomes	In line with NICE reference case[18]
Synthesis of evidence on health effects	Systematic literature review identified TALAPRO-2 trial providing evidence for rPFS and OS for talazoparib with enzalutamide. MAIC of RCTs	In line with NICE reference case[18]

Factor	Details	Rationale
	(TALAPRO-2 and PROpel) provided indirect comparative rPFS and OS data for talazoparib with enzalutamide versus olaparib with abiraterone based on studies identified in the systematic literature review.	
Measuring and valuing health effects	Health effects expressed in terms of QALYs using EQ-5D-3L	EQ-5D is the preferred measure of HRQoL, in line with NICE reference case,[18] and consistent with TA951[19]
Source of data for measurement of HQRoL	Progression-free: EQ-5D-5L data collected directly from patients in TALAPRO-2 trial mapped to EQ-5D-3L. Progressed disease: TA377.[25]	Progression-free: In line with NICE reference case,[18] and consistent with TA951[19]Progressed disease: Trial-based EQ-5D data were limited by low number of observations from Week 53 onwards, and TA951 values are redacted.[19] The approach used is therefore aligned to TA377, a NICE TA for mCPRC.[25]
Evidence on resource use and costs	Costs relate to NHS resource use and drug costs, valued using NHS reference costs, eMIT and BNF drug prices.[26–28]	In line with NICE reference case,[18] and consistent with TA951[19]

Abbreviations: BNF – British National Formulary; CUA – Cost-utility analysis; EAG – Expert advisory group; eMIT – Electronic market information tool; EQ-5D – EuroQoL 5-Dimensions; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; MAIC – Matching adjusted indirect comparison; OS – Overall survival; PD – Progressed disease; PSS – Personal Social Services; QALY – Quality-adjusted life year; RCT – Randomised control trial; rPFS – Radiographic progression-free survival; TA – Technical appraisal

2.1.1 Patient population

The population evaluated is in line with the technology's full marketing authorisation and the population assessed in TALAPRO-2 (Cohort 1, all-comers): adult patients with mCRPC for whom chemotherapy is not clinically indicated.

2.1.2 Perspective

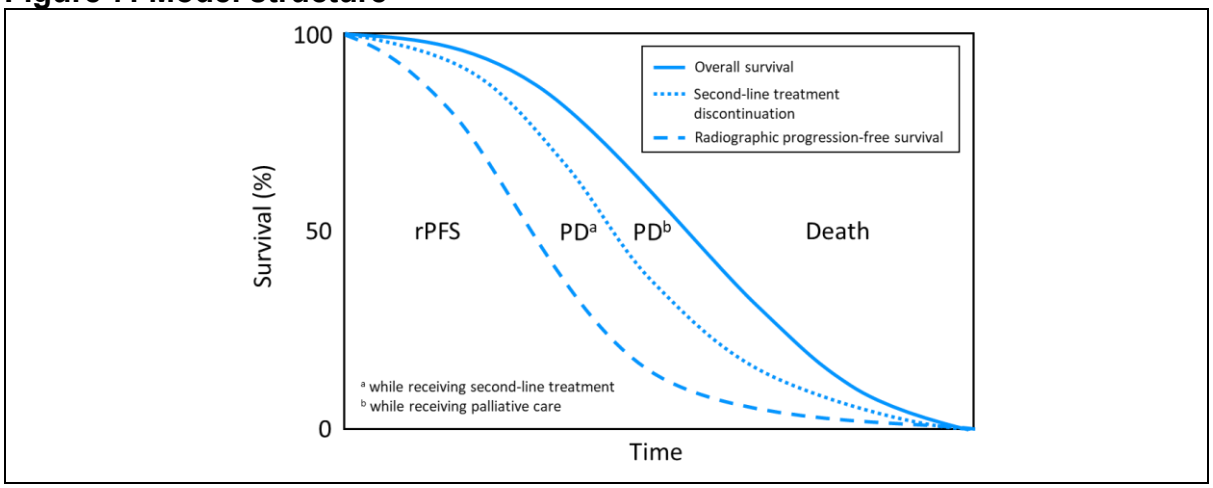
The analysis adopts a National Health Service (NHS) and Personal Social Services (PSS) perspective in England and Wales, hence all health effects for patients are considered in line with the NICE reference case.[18]

2.1.3 Model structure

The CUA, developed in Microsoft Excel®, utilises a partitioned survival model (PSM) structure with three mutually exclusive health states: rPFS, progressive disease (PD), and death, as illustrated in **Figure 7**. All patients enter the model in the rPFS health state and transition to the PD health state upon disease progression. The PD health state is split by time spent receiving subsequent treatment and time spent receiving palliative care. The death state is an absorbing state, meaning patients cannot transition out of the health state upon entering.

In each cycle, the PSM distributes patient state occupancy based on the treatment-specific parametric survival curves for rPFS and OS for the duration of the time horizon. The PD health state is delineated by receipt of subsequent treatment or palliative care. However, parametric survival curves for subsequent treatment time-to-discontinuation (TTD) are unavailable. Therefore, the model delineates the health state by approximating a curve subsequent treatment TTD that falls between the rPFS and OS curves. The proportion of time spent on subsequent treatment is calculated as the treatment-specific weighted average duration of subsequent therapy (see **Section 2.4.4.1**) divided by the difference between the (model-estimated) treatment-specific median rPFS and median OS. The proportion of time spent on subsequent treatment is then multiplied by the difference of the rPFS and OS parametric survival curves values at each cycle to determine the subsequent treatment TTD.

Figure 7: Model structure



Abbreviations: PD – Progressive disease; rPFS – Radiographic progression-free survival

Costs and health effects were calculated over a lifetime time horizon (consistent with TA951[19] and assumed to be 30 years based on the median age of 70.6 years in TALAPRO-2),[5] which is long enough to capture the difference in costs and health effects of treatment for patients with mCRPC, as per NICE guidelines.[18] A one-month model cycle length was used to accommodate the administration schedule of treatment regimens, whilst allowing sufficient granularity to accurately capture differences in cost and health effects between cycles. The model includes a half-cycle correction to account for progression and death events that occur during the one-month cycle, and to mitigate the risk of under- or over-estimating costs and effects. The half-cycle correction was not applied to treatment acquisition costs, as per EAG preference in TA951.[19]

A discount rate of 3.5% was applied to costs and health effects, in line with NICE guidelines.[18] Unit costs were sourced from the British National Formulary (BNF; 2024 or 2022 adjusted for inflation where necessary),[27] the electronic Market Information Tool (eMIT) National Database (2024),[28] and the National Schedule of NHS Costs (2023-2024; as the most recent available). The ONS Health CPI Index was adopted for the inflation to 2024 costs in the model.[32]

2.1.4 Intervention technology and comparators

The intervention of interest is talazoparib with enzalutamide and the comparator of interest is olaparib with abiraterone, consistent with the decision problem addressed in the original CS (see **Document B, Section B.1.1**).

2.2 *Clinical parameters and variables*

2.2.1 Summary of approach for rPFS and OS

To address the EAG's concerns that the PH assumptions for rPFS and OS may not hold in the Cox NMA in the original CS, individual survival analyses for rPFS and OS were required to estimate movement between health states. Survival analysis involved fitting parametric functions to the TALAPRO-2 and PROpel data to estimate long-term extrapolations for talazoparib with enzalutamide and olaparib with abiraterone, respectively.[5] The talazoparib with enzalutamide data were weighted via a MAIC, which matched and adjusted patient-level data from the TALAPRO-2 all-comers population to aggregate data from PROpel based on key prognostic factors and treatment stratification factors (**Section 1.2.1.2**).[8,9]

In line with the recommendation in DSU Technical Support Document (TSD) 14[33], independent models were fitted to each arm in the model, using the following distributions: log-normal, log-logistic, gamma, generalised gamma, Weibull, exponential, and Gompertz. The curve selection process involved an assessment of (1) statistical fit via Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), (2) visual fit compared to the KM curve, (3) comparison to the median survival estimates from TALAPRO-2,[5] (4) clinical plausibility of long-term survival estimates, and, most importantly (5) external validation/assessment against TA951 (olaparib with abiraterone in the same indication as this appraisal).

In TA951, six UK clinical experts with experience of using abiraterone for treating first-line mCRPC were consulted to clinically validate the appropriate choice of extrapolation.[19] The company selected the generalised gamma distribution in the

revised base case for both rPFS and OS following diagnostic, visual, statistical fit and hazard function assessments, and clinical expert validation.[19] The committee also concluded that the generalised gamma was the most appropriate parametric curve for extrapolating rPFS and OS.[19]

Given that TA951 followed a robust approach with extensive clinical expert input and EAG and NICE committee ratification[19], the approach to curve selection in this appraisal was to follow the NICE DSU TSD14 methodology to assess whether the TA951 base case curves (generalised gamma)[19] would be appropriate for rPFS and OS for both the talazoparib with enzalutamide arm and the olaparib with abiraterone arm. This approach to use the same curve for both arms was considered appropriate because of the similar mechanism of actions of talazoparib with enzalutamide and olaparib with abiraterone, and, as per TSD14, '*similar types of models (with 'type' defined as the same parametric distribution) should be used for the different treatment arms unless there is strong evidence to suggest an alternative is more plausible*'.[33]

In addition to validating the generalised gamma curve choice for the base case, the processes outlined in TSD14 were also used to identify plausible alternative curves for assessment in scenario analyses (**Section 2.8.3**). Covariance matrices were also developed for the survival curves, which form the basis of the probabilistic sensitivity analysis (PSA).

2.2.2 rPFS modelling

2.2.2.1 Talazoparib with enzalutamide

As described in **Section 1.2.1**, a MAIC was conducted to generate comparative effectiveness estimates for talazoparib with enzalutamide versus olaparib with abiraterone. The MAIC used TALAPRO-2 patient-level data, and generated MAIC-weighted rPFS KMs for use in the model.[5]

The goodness-of-fit statistics of all the distributions for rPFS for talazoparib with enzalutamide are presented in **Table 10**. Based on the AIC and BIC statistics, the log-

normal distribution provides the best statistical fit. The generalised gamma distribution is also a reasonable statistical fit as it is within four AIC points of the best fitting curve.[34]

In terms of landmark estimates, all curves provide [redacted] at 12 months, 24 months, 36 months, and 48 months, with a range of approximately [redacted] between the most conservative and optimistic curves. All curves provide similar estimates for median rPFS, with the log-normal, generalised gamma, and log-logistic curves providing the most accurate estimate relative to the trial KM curve.

Table 10: Goodness-of-fit statistics for talazoparib with enzalutamide rPFS parametric distributions, base case

Distribution	Goodness-of-fit				rPFS				
	AIC	BIC	Sum of AIC and BIC	Sum rank	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)
KM data									
Log-normal									
Generalised gamma									
Log-logistic									
Exponential									
Gamma									
Gompertz									
Weibull									

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; rPFS – Radiographic Progression-free survival

Figure 8 presents the talazoparib with enzalutamide rPFS parametric survival extrapolations and KM curve. The visual fit of the curves all provide a similar survival estimation, reaching the median rPFS at a similar time-point to the TALAPRO-2 KM curve.

Figure 8: KM for rPFS overlaid with extrapolated parametric survival curves, base case

Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; rPFS – Radiographic progression-free survival; TALA – Talazoparib; TP-2 – TALAPRO-2

In TA951, the company, EAG, and NICE committee preferred the generalised gamma curve for the base case.[19] The generalised gamma was selected in TA951 as it had the second best statistical fit, was more conservative than the best statistical fitting curve, allows for flexibility in capturing any differences in the underlying hazard function, and was considered by 6 UK clinical experts to provide the most clinically plausible long-term estimates.[19] The EAG considered the company's choice of generalised gamma to be appropriate based on the relative maturity of the rPFS data and the small differences in statistical fit between the best-fitting curves.[19]

Therefore, based on external validation from TA951 (which used 6 UK experts to determine curve choice),[19] statistical fit, visual fit, and landmark estimates, the company base case rPFS curve is generalised gamma. The log-normal and log-logistic curves are plausible alternatives to consider for scenarios based on their goodness-of-fit statistics and alignment to the observed KM median rPFS data.

2.2.2.2 Olaparib with abiraterone

As noted above, in TA951, the committee concluded that the generalised gamma was the most appropriate parametric curve for extrapolating OS and rPFS.[19] Therefore, the approach to curve selection in this appraisal was to use the TSD14 process to confirm and validate that the generalised gamma distribution is appropriate for modelling rPFS and OS for olaparib with enzalutamide in this appraisal.

The goodness-of-fit statistics for the rPFS for olaparib with abiraterone are presented in **Table 11**. Based on the AIC and BIC statistics, the log-logistic distribution provides the best statistical fit and may therefore also be appropriate for decision-making as an alternative to the generalised gamma distribution; this is aligned with the EAG's opinion in TA951.[19] All curves, except the Gompertz distribution, are a reasonable statistical fit, as they are within four AIC points of the best fitting curve.[34] All curves provide [redacted] landmark estimates at 12 and 24 months, with a [redacted] between the most conservative and optimistic curves. All curves provide [redacted] estimates for median rPFS, with the log-normal and exponential curves providing the most accurate estimate.

Table 11: Goodness-of-fit statistics for olaparib with abiraterone rPFS parametric distributions

Distribution	Goodness-of-fit					rPFS		
	AIC	BIC	Sum of AIC and BIC	Sum rank	Median (months)	12 months (%)	24 months (%)	48 months (%)
TA951 base case (generalised gamma)	-	-	-	-	23.0	NR	NR	28.2%
KM data								
Log-normal								
Generalised gamma								
Log-logistic								
Gamma								
Weibull								
Exponential								
Gompertz								

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; NR – Not reported; rPFS – Radiographic Progression-free survival

The olaparib with abiraterone rPFS parametric survival extrapolations and KM curve are presented in **Figure 9**. Other than the exponential distribution, the visual fit of the curves all provide a similar survival estimation, reaching median rPFS at a similar time-point to the KM curve.

Figure 9: Olaparib with abiraterone KM for rPFS overlaid with extrapolated parametric survival curves

Abbreviations: ABI – Abiraterone; KM – Kaplan-Meier; OLA – Olaparib; rPFS – Radiographic progression-free survival

In TA951, generalised gamma was selected for the base case rPFS and OS extrapolation due to statistical fit, visual fit, flexibility to capture variations in the underlying hazard function, and clinical plausibility as determined by 6 UK clinical experts.[19]

Based on validation from TA951, statistical fit, visual fit, and landmark estimates, the company base case curve choice is the generalised gamma distribution for rPFS. Plausible scenario analyses include log-normal and log-logistic given their good statistical fit and use in scenario analyses in TA951.[19]

2.2.3 OS modelling

2.2.3.1 Talazoparib with enzalutamide

As described in **Section 2.2.2.1**, a MAIC was conducted to generate weighted OS KMs for use in the model.

The goodness-of-fit statistics for the OS endpoint for talazoparib with enzalutamide are presented in **Table 12**. Based on the AIC and BIC statistics, the log-normal distribution provides the best statistical fit. The generalised gamma and log-logistic distributions are a reasonable statistical fit as they are within four AIC points of the best fitting curve.[34]

In terms of landmark estimates, all curves provide [redacted] estimates at 12 months, 24 months, 36 months, 48 months, and 60 months, with a [redacted] between the most conservative and optimistic curves. All curves provide similar estimates for median OS, with the log-logistic curve providing the most accurate estimate relative to the trial KM curve.

Table 12: Goodness-of-fit statistics for talazoparib with enzalutamide OS parametric distributions, base case

Distribution	Goodness-of-fit				OS						
	AIC	BIC	Sum of AIC and BIC	Sum rank	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data											
Log-normal											
Log-logistic											
Generalised gamma											
Gamma											
Weibull											
Gompertz											

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; OS – Overall survival

The talazoparib with enzalutamide OS parametric survival extrapolations and KM curve are presented in **Figure 10**. Other than the exponential and Gompertz distributions, the visual fit of the curves all provide a similar survival estimation, reaching the median OS at a similar time-point to the TALAPRO-2 KM curve.

Figure 10: KM for OS overlaid with extrapolated parametric survival curves, scenario, base case

Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; OS – Overall survival; TALA – Talazoparib; TP-2 – TALAPRO-2

In TA951, the company, EAG, and committee preferred generalised gamma for the base case OS extrapolation.[19] The company selected generalised gamma due to good statistical fit, good fit to the observed KM data, plausibility of landmark survival estimates as agreed with 6 UK clinical experts, and because it has the flexibility to account for differing hazard functions over time.[19] Clinical advice to the EAG was that log-logistic may be more appropriate due to more plausible long-term landmark estimates.[19] Based on further clinical expert discussion, the committee concluded that generalised gamma was the most appropriate parametric curve for extrapolating OS in TA951.[19]

Therefore, based on validation against TA951, statistical fit, visual fit, and plausibility of landmark estimates, the company base case OS curve choice for the talazoparib with enzalutamide arm is generalised gamma. Plausible scenarios include log-logistic and log-normal, given their statistical and visual fit to the data.

2.2.3.2 Olaparib with abiraterone

For OS, based on the AIC and BIC statistics, the log-normal distribution provides the best statistical fit and therefore may also be appropriate for decision-making as an alternative to the generalised gamma distribution; this is also aligned with the EAG's opinion in TA951.[19] The log-logistic distribution is also a reasonable statistical fit as it is within four AIC points of the best fitting curve.[34] All curves provide [redacted] landmark estimates at 12, 24, and 36 months, with a range of approximately [redacted] at 12 months which narrows at 24 and 36 months. While median OS was not reached in the trial data, all curves provide similar estimates for median OS.

Table 13: Goodness-of-fit statistics for olaparib with abiraterone OS parametric distributions

Distribution	Goodness-of-fit					OS					
	AIC	BIC	Sum of AIC and BIC	Sum rank	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
TA951 base case (gen gamma)	-	-	-	-	43.0	87.7%	70.5%	NR	46.2%	Not reported	17.1%
KM data											
Log-normal											
Generalised gamma											
Log-logistic											
Gamma											
Weibull											
Exponential											
Gompertz											

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; NR – Not reached; OS – Overall survival

The olaparib with abiraterone OS parametric survival extrapolations and KM curve are presented in **Figure 11**. Other than the exponential distribution, the visual fit of the curves all provide a similar survival estimation, reaching the median rPFS at a similar time-point to the KM curve and providing similar median OS estimations.

Figure 11: Olaparib with abiraterone KM for OS overlaid with extrapolated parametric survival curves

Abbreviations: ABI – Abiraterone; KM – Kaplan-Meier; OLA – Olaparib; OS – Overall survival

In TA951, generalised gamma was selected for the base case rPFS and OS extrapolation due to statistical fit, visual fit, flexibility to capture variations in the underlying hazard function, and clinical plausibility as determined by 6 UK clinical experts.[19]

In TA951, 87.7%, 70.5%, 46.2%, and 17.1% of patients treated with olaparib with abiraterone were estimated to be alive at years 1, 2, 4, and 10 when using the generalised gamma extrapolation.[19] In the current model for this appraisal, an estimated [redacted]%, [redacted]%, [redacted]%, and [redacted]% of patients treated with olaparib with abiraterone are estimated to be alive at years 1, 2, 4, and 10 when using the

generalised gamma extrapolation. The similarity in landmark estimates confirms that generalised gamma is appropriate for the olaparib with abiraterone arm of this appraisal.

Based on validation from TA951, statistical fit, visual fit, and landmark estimates, the company base case OS curve choice is generalised gamma. Plausible scenarios include log-normal and log-logistic, due to statistical and visual fit and alignment with TA951.

2.2.4 Summary of base case inputs for rPFS and OS

The data sources and chosen distributions to inform the base case analysis are presented in **Table 14**. **Figure 12** to Error! Reference source not found. below present the modelled base case curves for rPFS and OS.

Table 14: Summary of base case survival analysis inputs

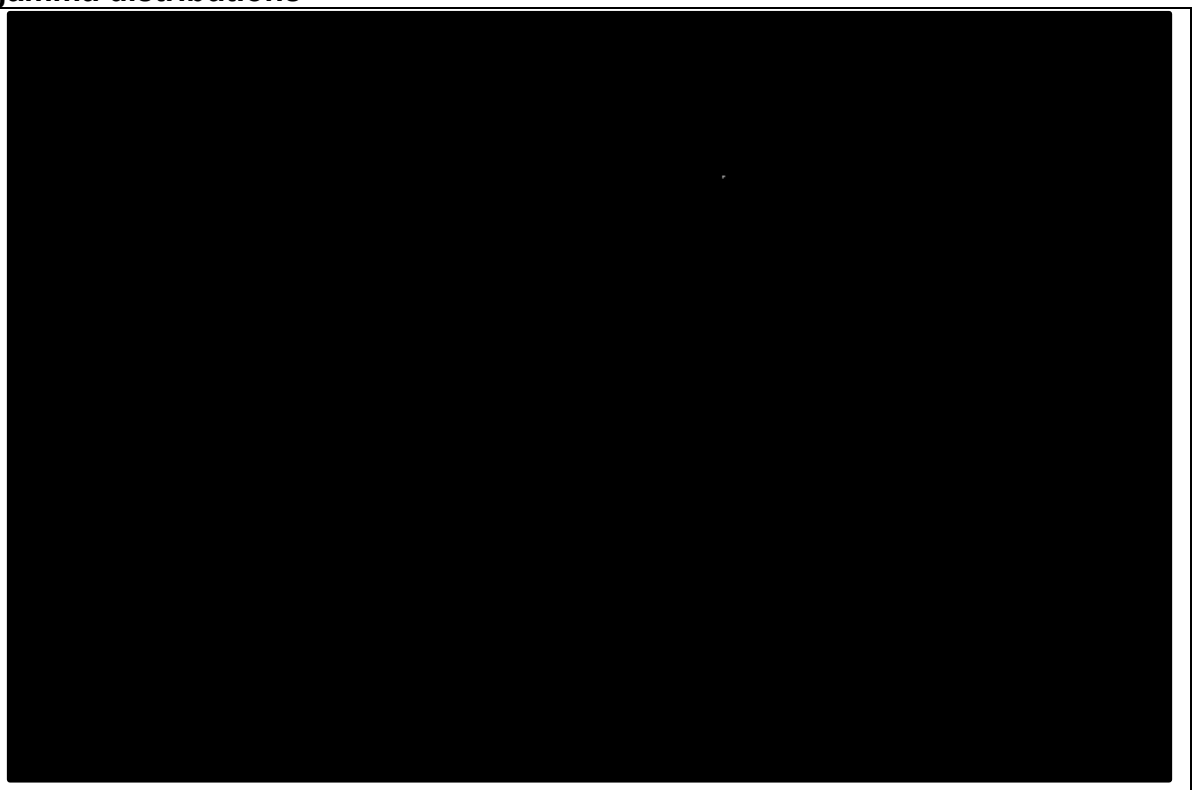
Treatment arm	Clinical parameter	Data source	Chosen distribution
TALA+ENZA	rPFS	MAIC-weighted TALAPRO-2 data	Generalised gamma
	OS		Generalised gamma
OLA+ABI	rPFS	PROpel data	Generalised gamma
	OS		Generalised gamma

Abbreviations: MAIC – Match-adjusted indirect comparison; OLA+ABI; Olaparib with abiraterone; OS – Overall survival; rPFS – Radiographic progression-free survival; TALA+ENZA – Talazoparib with enzalutamide; TTD – Time-to-treatment discontinuation

Figure 12: Talazoparib with enzalutamide and olaparib with abiraterone KMs for rPFS overlaid with the extrapolated parametric survival curves using generalised gamma distributions

Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; rPFS – Radiographic progression-free survival; TALA - Talazoparib

Figure 13: Talazoparib with enzalutamide and olaparib with abiraterone KMs for OS overlaid with the extrapolated parametric survival curves using generalised gamma distributions



Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; OS – Overall survival; TALA - Talazoparib

Figure 14: Talazoparib with enzalutamide and olaparib with abiraterone KMs for rPFS and OS overlaid with the extrapolated parametric survival curves using generalised gamma distributions

Abbreviations: ABI – Abiraterone; KM – Kaplan-Meier; OLA – Olaparib; rPFS – Radiographic progression-free survival

2.2.5 Treatment duration modelling

2.2.5.1 Talazoparib with enzalutamide

At the time of submitting this addendum, TTD data from the latest data cut of TALAPRO-2 is being processed. As such, the model assumes that TTD is equal to rPFS for talazoparib with enzalutamide (using gen gamma distribution). The company expect TTD data to be available and incorporated into the analysis for the EAG clarification questions stage.

2.2.5.2 Olaparib with abiraterone

Detailed TTD KMs from PROpel are not available. However, landmark estimates from PROpel are available from the CADTH submission for olaparib with abiraterone.[35] Additionally, PROpel rPFS KM was estimated using the rPFS KM curve reported in Clarke et al. 2022.[9] As shown in **Table 15**, there is consistency between TTD and rPFS in PROpel, which supports the assumption that TTD is equal to rPFS for olaparib

with abiraterone. The model base case therefore assumes that TTD is equal to rPFS for olaparib with abiraterone.

Table 15: Comparison of trial TTD and model rPFS for olaparib with abiraterone

Distribution	TTD/rPFS		
	12 months (%)	24 months (%)	36 months (%)
PROpel TTD KM	74.0%	51.0%	47.0%
Clarke et al. 2022 rPFS KM[9]	73.7%	53.8%	-
Model-estimated rPFS (gen gamma)	[redacted]	[redacted]	[redacted]

Note: PROpel rPFS data was estimated using the rPFS KM reported in Clarke et al. 2022[9].
Abbreviations: KM – Kaplan Meier; rPFS – radiographic progression-free survival; TTD – Time to discontinuation

2.2.6 Mortality

Extrapolated OS curves for talazoparib with enzalutamide and olaparib with abiraterone were adjusted for general population mortality informed by life tables for the UK to ensure the disease-related risk of death does not exceed general population estimates.[36]

2.3 *Measurement and valuation of health effects*

Patients with mCRPC typically experience worse health-related quality of life (HRQoL) compared to the general population across several domains including symptom and morbidity burden – see **Document B, Section B.1.3.1** for further information.

2.3.1 Health-related quality-of-life data from clinical trials

HRQoL was measured in TALAPRO-2 using EQ-5D-5L. Patients were asked to complete the EQ-5D-5L health questionnaire at the following timepoints: Baseline (day 1); every 4 weeks through Week 53 or radiographic progression, whichever is earlier; every 8 weeks after Week 53 until radiographic progression when no such progression had been previously documented; every 12 weeks after centrally determined radiographic progression until end of study.[3] In the model, health state utilities for rPFS were estimated using the individual patient-level EQ-5D-5L data from TALAPRO-2.[3]

In TALAPRO-2 cohort 1 at the 28 March 2023 data cutoff date (the data cut used for the utility analysis), there were a total of [redacted] pre-progression EQ-5D observations

across both treatment arms and a total of [redacted] post-progression observations.[3] As expected, the number of observations [redacted]. The high degree of missing data and low number of observations for patients in post-progression means that the post-progression trial data are not robust for use in the model.

2.3.2 Mapping

To generate rPFS health state utilities, the EQ-5D-5L indices were mapped to the EQ-5D-3L indices using the crosswalk algorithm described by Hernandez-Alava et al. 2022, in line with the NICE reference case.[18,37] The economic model uses the mapped EQ-5D-3L values to estimate the health state utility of patients in the rPFS health state.

A linear mixed model was used to predict EQ-5D utilities. As the outcome was not assessed in a single follow-up, but in different follow-up timepoints (weeks) in the TALAPRO-2 trial, an analysis of repeated measures was conducted. The EQ-5D-5L utility values for mCRPC patients from the TALAPRO-2 trial were calculated at each different timepoint/follow-up period. This approach appropriately considers utilities over time and accounts for correlations between repeated utility values at different timepoints for the same patient. Within the mixed model, random effects as well as several fixed effects were considered, including planned treatment, time of visit (since randomisation), age, baseline utility, baseline Eastern Cooperative Oncology Group (ECOG) status, planned treatment, and an interaction term between planned treatment and health state. Patients were included as a random effect in the model.

2.3.3 Health-related quality-of-life studies

An SLR was conducted to identify studies reporting on the HRQoL of patients with mCRPC. The SLR was originally conducted in August 2021 and updated in October 2022, and in line with the pragmatic approach agreed with NICE, an update for the purposes of this appraisal has not been conducted. Instead, utility values are derived from TALAPRO-2, as well as relevant NICE appraisals in mCRPC (i.e., TA951 and TA377).[19,25] A targeted search also revealed no additional HRQoL data that could be used in the model.

2.3.4 Age-adjusted utilities

The economic model includes an age-related adjustment to account for QoL deterioration with age. Age-adjusted utilities were implemented using the methods described in Hernandez-Alava (2022) and applied to each model cycle for the full model time horizon.[37]

2.3.5 Adverse reactions

2.3.5.1 Adverse events

AE data were sourced from the TALAPRO-2 and PROpel clinical trials for the talazoparib with enzalutamide and olaparib with abiraterone arms, respectively.[5,8] In line with the original CS, the CUA accounts for the impact of all grade ≥3 treatment-related AEs occurring in ≥5% of patients receiving treatment across either treatment arm of their respective studies. Events occurring in ≥5% of patients were considered appropriate to capture AEs that would impact patients in a real-world setting, where AEs are monitored in a less strict manner compared to a clinical trial setting. The AEs included in the model are reported in **Table 16**.

As mentioned in **Section 1.3** of the original CS**,** UK clinical experts consulted by the company stated that they would likely manage grade ≥3 AEs more proactively in clinical practice than was allowed in TALAPRO-2. They also stated that anaemia from the use of PARP inhibitor + NHA combination is expected and easily detectable in practice. The rate of grade ≥3 anaemia and associated discontinuation would therefore likely be lower in real-world practice than observed in TALAPRO-2. The model is therefore conservative in terms of AEs and associated costs.

Table 16: Frequencies of Grade ≥3 treatment-related AEs occurring in ≥5% of patients by treatment

Adverse event	Frequency	
	Talazoparib with enzalutamide	Olaparib with abiraterone
Anaemia	[redacted]	16.1%
Leukopenia	[redacted]	0.0%
Neutropenia	[redacted]	4.8%
Thrombocytopenia	[redacted]	0.0%
Venous thromboembolic event	[redacted]	7.8%

Source: TALAPRO-2 trial and PROpel trial (Saad et al. 2023)[3,8]

Table 17 presents the AE-specific disutilities, their corresponding durations, and sources. With the exception of thrombocytopenia, all AE disutilities and durations were consistent with TA951.[19] AE disutilities are applied in the rPFS health state for the duration of each respective AE.

Table 17: Adverse events disutilities and duration estimates

Adverse event	Disutility	Duration (days)	Source
Anaemia	−0.020	14.00	NICE (TA951, Table 35)[19]
Leukopenia	−0.020	14.00	NICE (TA951, Table 35)[19]
Neutropenia	−0.020	14.00	NICE (TA951, Table 35)[19]
Thrombocytopenia	−0.066	14.00	(Diaby et al., 2016).[38] Duration was not reported, so assumed to be 14 days, consistent with other AEs.
Venous thromboembolic event	−0.051	14.00	Based on disutility for pulmonary embolism. NICE (TA951, Table 35)[19]

Abbreviations: AE – Adverse event; NICE – National Institute for Health and Care Excellence

2.3.5.2 Skeletal-related events

SRE data were sourced from TALAPRO-2 for talazoparib with enzalutamide and from TA951 for olaparib with abiraterone.[5,19] The SREs included in the model are reported in **Table 18**.

Table 18: Frequencies of SREs by treatment

Skeletal-related event	Frequency	
	Talazoparib with enzalutamide	Olaparib with abiraterone
Spinal cord compression	[redacted]	15.5%
Radiation to bone	[redacted]	67.7%
Surgery to bone	[redacted]	4.1%
Pathologic bone fracture	[redacted]	12.9%

Abbreviations: SRE – Skeletal-related event
Source: TALAPRO-2[3] and TA951[19]

Disutilities related to SREs were applied as a one-time decrement, with decrement estimates and durations consistent with TA951.[19] **Table 19** presents the SRE disutilities used in the model.

Table 19: SRE disutilities

Skeletal-related event	Disutility	Duration (days)	Source
Spinal cord compression	-0.555	30.44	NICE (TA951, Table 35)[19]
Radiation to bone	-0.070	30.44	
Surgery to bone	-0.130	30.44	
Pathologic bone fracture	-0.130	30.44	

Abbreviations: NICE – National Institute for Health and Care Excellence; SRE – Skeletal-related event

2.3.6 Health-related quality-of-life data used in the cost-effectiveness analysis

In the model, the rPFS health state utility value is based on pooled data from both treatment arms of TALAPRO-2[39]. This utility value [redacted] with the rPFS values identified in a systematic review for TA951 (0.844 from PREVAIL trial for enzalutamide, and 0.830 from COU-AA302 trial for abiraterone).

Health state utilities for PD (while receiving subsequent treatment and palliative care) were taken from TA377, a previously published NICE health technology assessment in mCRPC.[25] As per the approach in TA377, the base case adopts a PD utility value of 0.658 when receiving subsequent treatment and a PD utility value of 0.500 for post-subsequent treatment (palliative care).[25]

Table 20 presents a summary of the utilities used in the cost-effectiveness analysis.

Table 20: Summary of utilities for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Justification
Health states			
rPFS (pooled data from TALAPRO-2)	[redacted]	[redacted]	Mapped EQ-5D-3L values directly measured from the TALAPRO-2 study population
PD (on subsequent treatment)	0.658 (0.007)	0.574, 0.741	Values not available from TALAPRO-2, so post-progression population values from TA377 are used (TA377 is in metastatic hormone-relapsed prostate cancer)[25]
PD (post-subsequent treatment, palliative care)	0.500 (0.080)	0.344, 0.656	
Adverse events			
Anaemia	−0.020 (0.009)	−0.002, −0.038	Values were not available in the TALAPRO-2 study, so values from TA951 are used (TA951 is the same indication as this appraisal)[19]
Leukopenia	−0.020 (0.009)	−0.002, −0.038	
Neutropenia	−0.020 (0.009)	−0.002, −0.038	
Thrombocytopenia	−0.066 (0.013)	−0.059, −0.073	Values were not available in TALAPRO-2, so value is based on Diaby et al. 2016 cost-effectiveness analysis for metastatic breast cancer[38]
Venous thromboembolic event	−0.051 (0.013)	−0.026, −0.076	Value was not available in the TALAPRO-2 study, so the value from TA951 is used (TA951 is the same indication as this appraisal)[19]
Skeletal-related events			
Spinal cord compression	-0.555	−0.500, −0.610	Values were not available in the TALAPRO-2 study, so values from TA951 are used (TA951 is the same indication as this appraisal)[19]
Radiation to bone	-0.070	−0.063, −0.077	
Surgery to bone	-0.130	−0.117, −0.143	
Pathologic bone fracture	-0.130	−0.117, −0.143	

Abbreviations: EQ-5D-3L – European Quality of Life 5 Dimensions 3 Level; PP2 – Post-progression 2

2.4 *Cost and healthcare resource use identification, measurement and valuation*

2.4.1 Intervention and comparators' costs and resource use

2.4.1.1 Drug acquisition costs

Drug acquisition costs were based on the dosing regimens presented in **Table** 21. Costs per pack and cycle are presented in **Table 22**. Dosing information was aligned with each drug's respective SmPC. The unit costs were sourced from the BNF and eMIT[28]. A PAS discount of [redacted] is applied to talazoparib. The half-cycle correction is not applied to treatment acquisition costs, as per the EAG preference in NICE TA951.[19]

Patients receiving talazoparib with enzalutamide were treated in line with the modelled TTD curve. All RDI values are conservatively assumed to be 100%. The company is currently conducting a post-hoc dose reduction analysis on the most recent data cut from TALAPRO-2 (3rd September 2024) to determine the median RDI for talazoparib with enzalutamide. The results are expected to be available and incorporated into the analysis for the EAG clarification questions stage.

Table 21: Dosing regimen of treatments included in the economic model

Treatment	Dosing regimen	Source
Talazoparib	0.5 mg once per day	BNF[27]
Enzalutamide	160 mg once per day	BNF[27]
Olaparib	300 mg twice per day	Lynparza SmPC (2023)[40]
Abiraterone acetate	1,000 mg once per day	Lynparza SmPC (2023)[40]
Prednisolone	5 mg twice per day	Lynparza SmPC (2023)[40]

Abbreviations: mg – Milligram; SmPC – Summary of product characteristics

Table 22: Drug package price and cost per cycle

Treatment	Dose (mg per unit)	Daily dose (mg)	Pack size	Administration route	Cost per pack (£)	Cost per cycle (£)	Source
Talazoparib	0.25	0.5	30	Oral	1,655.00	[redacted]	BNF, 2024[27]
Enzalutamide	40	160	112	Oral	2,734.67	2,972.73	
Olaparib	150	600	56	Oral	2,317.50	5,038.49	
Abiraterone acetate	500	1,000	56	Oral	76.91	83.60	eMIT, 2024[28]
Prednisolone	5	10	28	Oral	0.41	0.89	

Abbreviations: BNF – British National Formulary; eMIT – Electronic market information tool; mg - Milligram

2.4.1.2 Drug administration costs

Medications that are orally administered were assumed not to incur administration costs. Administration costs were included for subsequent treatments administered by intravenous (IV) infusion (see **Section 2.4.4.1**), sourced from the National Schedule of NHS Costs (2023/24) and aligned with TA951.[19,26]

Table 23: Drug administration costs

Treatment	Administration cost (£)	Source	NHS currency code
Docetaxel	201.66	National Schedule of NHS Costs (2023/24)[26]	SB13Z
Cabazitaxel	201.66		SB13Z
Radium-223	201.66		SB13Z
Carboplatin	201.66		SB13Z

Abbreviations: NHS – National Health Service

The model also considers wastage for IV drugs as there is a possibility that some of the drug will be wasted if perfect vial sharing is not practiced. No wastage is assumed to occur for oral treatments as patients would receive the exact number of tablets or capsules they need for treatment.

2.4.2 Health-state unit costs and resource use

Costs related to routine follow-up and disease management were calculated by multiplying the resource use per cycle by the unit cost for each resource item. Drug and disease monitoring unit costs are sourced from the National Schedule of NHS Costs for 2023/24, as recommended by the NICE reference case.[18,26]

2.4.2.1 Drug monitoring costs and resource use

Frequency of resource use is based on the respective drug SmPCs. Drug monitoring costs and resource use are differentiated by treatment phase (initiation and during treatment) and are presented for talazoparib with enzalutamide in **Table 24**. In the base case, olaparib with abiraterone is assumed to incur the same drug monitoring requirements as talazoparib with enzalutamide, in line with the EAG's preference in the original CS. This is a conservative assumption given that olaparib with abiraterone is associated with greater monitoring requirements than talazoparib with enzalutamide, according to the product SmPCs. A scenario is therefore explored

where the olaparib with abiraterone resource use requirements are based on their SmPC (**Table 25**). The scenario results can be seen in **Section 2.8.3**.

Table 24: Drug monitoring unit costs and frequencies (talazoparib with enzalutamide)

Resource item	Costs			Resource use per cycle		
	Unit (£)	NHS currency/service code	Source	At treatment initiation	During treatment	Source
Complete blood count	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	1.0	1.0	Talzenna SmPC (2019)[41] and Xtandi SmPC (2022)[42]
Serum potassium assay test	3.10	PATH05		0.0	0.0	
Hepatic function panel	1.53	PATH04		0.0	0.0	
Office visit	193.89	370		0.0	0.0	
Electrocardiogram	641.76	EY51Z		0.0	0.0	

Abbreviations: NHS – National Health Service; SmPC – Summary of product characteristics

Table 25: Drug monitoring unit costs and frequencies (olaparib with abiraterone)

Resource item	Costs			Resource use per cycle			
	Unit (£)	NHS currency/service code	Source	At treatment initiation	First 3 months of treatment	Subsequent months of treatment	Source
Complete blood count	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	1.0	1.0	1.0	Lynparza SmPC (2023)[40] and Zytiga SmPC (2024)[43]
Serum potassium assay test	3.10	PATH05		0.0	1.0	1.0	
Hepatic function panel	1.53	PATH04		1.0	2.2	1.0	
Office visit	193.89	370		0.0	1.0	1.0	
Electrocardiogram	641.76	EY51Z		0.0	0.0	0.0	

Abbreviations: NHS – National Health Service; SmPC – Summary of product characteristics

2.4.2.2 Disease monitoring costs and resource use

In addition to treatment-specific costs, the model captures the costs of disease monitoring procedures every cycle while patients are in the rPFS health state or receiving subsequent treatment. The disease monitoring frequencies and proportions of patients undergoing disease monitoring were sourced from TA951, Talzenna SmPC (2019), and Xtandi SmPC (2022).[19,41,42] The disease monitoring costs and resource use for talazoparib with enzalutamide and olaparib with abiraterone are presented in **Table 26** and **Table 33**, respectively. A scenario is explored where the olaparib with abiraterone disease monitoring frequencies are equal to that of talazoparib with enzalutamide. The scenario results can be seen in **Section 2.8.3.**

Table 26: Disease monitoring resource use and costs (talazoparib with enzalutamide)

Resource item	Costs			Resource use per cycle				
	Unit (£)	NHS currency/service code	Source	First 3 months of treatment		Subsequent months of treatment		Source
				Proportion of patients (%)	Frequency	Proportion of patients (%)	Frequency	
Office visit (consultant led)	193.89	370	National Schedule of NHS Costs (2023/2024)[26]	50	2.175	50	1.088	NICE (TA951, table 45)[19]
Office visit (nurse led)	49.33	-	TA951[19]	50	2.175	50	1.088	
CT scan	121.39	Average of RD20A, RD21A, and RD22Z-RD27Z	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	2.175	
Bone scan	271.55	RN15A	National Schedule of NHS Costs (2023/2024)[26]	20	0.348	20	0.348	
Complete blood count	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	100	1.000	100	1.000	Talzenna SmPC (2019)[41] and Xtandi SmPC (2022)[42]
Liver function test	1.53	PATH04	National Schedule of NHS Costs (2023/2024)[26]	0	0.000	0	0.000	
Kidney function test	3.10	PATH05	National Schedule of	0	0.000	0	0.000	

Resource item	Costs			Resource use per cycle				
	Unit (£)	NHS currency/service code	Source	First 3 months of treatment		Subsequent months of treatment		Source
				Proportion of patients (%)	Frequency	Proportion of patients (%)	Frequency	
			NHS Costs (2023/2024)[26]					
Treatment toxicity monitoring (first 12 months)	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	0	0.000	0	0.000	
Prostate specific antigen test	1.53	PATH04	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	1.088	

Abbreviations: CT – Computed tomography; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; SmPC – Summary of product characteristics; TA – Technology assessment

Table 27: Disease monitoring resource use and costs (olaparib with abiraterone)

Resource item	Costs			Resource use per cycle				
				First 3 months of treatment		Subsequent months of treatment		
	Unit (£)	NHS currency/ service code	Source	Proportion of patients (%)	Frequency	Proportion of patients (%)	Frequency	Source
Office visit (consultant led)	193.89	370	National Schedule of NHS Costs (2023/2024)[26]	50	2.175	50	1.088	NICE (TA951, table 45)[19]
Office visit (nurse led)	49.33	-	TA951[19]	50	2.175	50	1.088	
CT scan	121.39	Average of RD20A, RD21A, and RD22Z-RD27Z	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	2.175	
Bone scan	271.55	RN15A	National Schedule of NHS Costs (2023/2024)[26]	20	0.348	20	0.348	
Complete blood count	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	1.088	
Liver function test	1.53	PATH04	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	1.088	
Kidney function test	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	1.088	

Resource item	Costs			Resource use per cycle				
	Unit (£)	NHS currency/ service code	Source	First 3 months of treatment		Subsequent months of treatment		Source
				Proportion of patients (%)	Frequency	Proportion of patients (%)	Frequency	
Treatment toxicity monitoring (first 12 months)	3.10	PATH05	National Schedule of NHS Costs (2023/2024)[26]	100	1.001	100	1.001	
Prostate specific antigen test	1.53	PATH04	National Schedule of NHS Costs (2023/2024)[26]	100	2.175	100	1.088	

Abbreviations: CT – Computed tomography; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; SmPC – Summary of product characteristics; TA – Technology assessment

2.4.3 Adverse reaction unit costs and resource use

AE and SRE costs were sourced from the National Schedule of NHS Costs (2023/2024).[26]

2.4.3.1 Adverse events

Total AE costs were calculated as the product of the AE incidence rate, presented in **Table 16**, and the unit cost, presented in **Table 28**. It is assumed that all AEs occur and are resolved in the first cycle of treatment.

Table 28: AE management costs

AE	One-time cost (£)	NHS currency/service code	Source
Anaemia	649.79	Assumed to be a non-elective short stay. Weighted average of the currency codes: SA04G, SA04H, SA04J, SA04K, SA04L	National Schedule of NHS Costs (2023/2024)[26]
Leukopenia	193.89	Assumed as outpatient cost (consultant led). Service code: 370	
Neutropenia	193.89		
Thrombocytopenia	193.89		
Venus thromboembolic event	193.89		

Abbreviations: AE – Adverse event; NHS – National Health Service

2.4.3.2 Skeletal-related events

SRE costs utilised in the model are consistent with TA951.[19] Total SRE costs were calculated as the product of the SRE incidence rate, presented in **Table 18**, and the unit cost, presented in **Table 29**. It is assumed that all SREs occur and are resolved in the first cycle of treatment.

Table 29: SRE management costs

SRE	One-time cost (£)	NHS currency code	Source
Spinal cord compression	7,848.26	Assumed to be non-elective inpatient long stay. Currency code: HC28J.	National Schedule of NHS Costs (2023/2024)[26]
Radiation to bone	1,015.04	Weighted average of the currency codes: SC21Z- SC28Z.	
Surgery to bone	5,140.57	Assumed to be non-elective inpatient long stay. Currency code: HD39E.	
Pathologic bone fractures	6,294.00	-	NICE (TA951, table 49)[19]

Abbreviations: NICE – National Institute for Health and Care Excellence; NHS – National Health Service; SRE – Skeletal-related event

2.4.4 Miscellaneous unit costs and resource use

2.4.4.1 Subsequent treatment costs

Subsequent treatment costs are applied when patients enter the PD health state.

The distribution of subsequent treatments is based on TA951.[19] In TA951, six clinical experts with experience of treating patients with mCRPC were consulted to determine the subsequent treatment distribution in UK clinical practice. The elicited experts indicated that most patients in the UK are treated with docetaxel and cabazitaxel following disease progression on an NHA. The experts also stated that retreatment with NHA or olaparib monotherapy is not permitted in UK clinical practice following disease progression on abiraterone or enzalutamide.[19] The insights from TA951 are applicable to talazoparib with enzalutamide given the similar mechanism of action to olaparib with abiraterone.

Talazoparib with enzalutamide and olaparib with abiraterone are therefore assumed to have the same subsequent treatment distribution, with values derived from TA951. The proportion of patients receiving each subsequent therapy is presented in **The** treatment durations for the subsequent treatments are based on published data and presented in **Table 32**. The weighted average subsequent treatment duration is obtained by summing the products of each treatment duration with its relative distribution. If the weighted duration is less than the difference in the talazoparib with

enzalutamide or olaparib with abiraterone median OS and rPFS, then the proportion of time spent receiving subsequent treatment in the PD health state is assumed to be equal to the weighted average subsequent treatment duration divided by the difference in the median OS and rPFS. If the weighted duration is greater than or equal to the difference in the median OS and rPFS, then patients are assumed to receive subsequent treatment for the entire time spent in the PD health state.

Table 30. Costs are sourced from the National Schedule of NHS Costs (2023/24), eMIT, and the BNF,[26–28] and are presented in **Table 31**. The treatment durations for the subsequent treatments are based on published data and presented in **Table 32**. The weighted average subsequent treatment duration is obtained by summing the products of each treatment duration with its relative distribution. If the weighted duration is less than the difference in the talazoparib with enzalutamide or olaparib with abiraterone median OS and rPFS, then the proportion of time spent receiving subsequent treatment in the PD health state is assumed to be equal to the weighted average subsequent treatment duration divided by the difference in the median OS and rPFS. If the weighted duration is greater than or equal to the difference in the median OS and rPFS, then patients are assumed to receive subsequent treatment for the entire time spent in the PD health state.

Table 30: Subsequent treatment distributions

Subsequent treatment	Talazoparib with enzalutamide	Olaparib with abiraterone	Source
Docetaxel	50.0	50.0	TA951[19]
Cabazitaxel	29.1	29.1	
Carboplatin	3.5	3.5	
Radium-223	17.5	17.5	

Table 31: Subsequent drug dosing and costs

Treatment	Dose per administration (mg)	Number of administrations per day	Administration route	Cost per cycle (£)	Source
Docetaxel	75 (mg/m^2)	-	IV	673.17	National Schedule of NHS Costs,[26] Taxotore SmPC, eMIT[28]
Prednisolone (in combination with docetaxel)	5	2	Oral	0.83	Taxotore SmPC,[44] eMIT[28]
Cabazitaxel	25 (mg/m^2)	-	IV	3,753.60	National Schedule of NHS Costs,[26] Jevtana SmPC,[45] BNF[27]
Prednisolone (in combination with cabazitaxel)	5	2	Oral	0.83	Jevtana SmPC,[45] eMIT[28]
Carboplatin	400 (mg/m^2)	-	IV	297.58	National Schedule of NHS Costs,[26] Carboplatin SmPC,[46] eMIT[28]
Radium-223 dichloride	55 (kBq/kg)	-	IV	2,879.62	National Schedule of NHS Costs,[26] Xofigo SmPC,[47] TA412[48]

Abbreviations: BNF – British National Formulary; eMIT – Electronic market information tool ; IV – Intravenous; kBq – Kilobecquerel; kg – Kilogram; m – Meter; MBq – Megabecquerel; Mg – Milligram; SmPC – Summary of product characteristics; TA – Technology appraisal

Table 32: Subsequent treatment durations

Treatment	Treatment duration (months)	Source
Docetaxel in combination with prednisolone	5.9	Tannock et al. (2004)[49]
Cabazitaxel in combination with prednisolone	5.1	de Wit et al. (2019)[50]
Radium-223 dichloride	5.5	Xofigo SmPC (2024)[47]
Carboplatin	2.1	Pemberton et al. (2024)[51]

Abbreviations: SmPC – Summary of product characteristics

The drug monitoring requirements for subsequent treatments are based on each drug's respective SmPC. The subsequent treatment drug monitoring requirements are presented in **Table 33**.

Table 33: Subsequent treatment drug monitoring resource use

Treatment	Resource item	Resource use per cycle				
		At treatment initiation	At first month of treatment	First 3 months of treatment	Subsequent months of treatment	Source
Docetaxel in combination with prednisolone	Complete blood count	1.5	-	-	1.5	Taxotere SmPC[44]
	Serum potassium assay test	0.0	-	-	0.0	
	Hepatic function panel	0.0	-	-	0.0	
	Office visit	0.0	-	-	0.0	
	Electrocardiogram	0.3	-	-	0.3	
Cabazitaxel in combination with prednisolone	Complete blood count	-	4.4	-	1.4	Jevtana SmPC[45]
	Serum potassium assay test	-	0.0	-	0.0	
	Hepatic function panel	-	0.0	-	0.0	
	Office visit	-	0.0	-	0.0	
	Electrocardiogram	-	0.0	-	0.0	
Carboplatin	Complete blood count	4.3	-	-	4.3	Carboplatin SmPC[46]
	Serum potassium assay test	2.2	-	-	2.2	
	Hepatic function panel	2.2	-	-	2.2	
	Office visit	0.0	-	-	0.0	
	Electrocardiogram	0.0	-	-	0.0	
Radium-223 dichloride	Complete blood count	1.0	-	-	1.1	Xofigo SmPC[47]
	Serum potassium assay test	0.0	-	-	0.0	
	Hepatic function panel	0.0	-	-	0.0	
	Office visit	0.0	-	-	0.0	
	Electrocardiogram	0.0	-	-	0.0	

Abbreviations: SmPC – Summary of product characteristics

2.4.4.2 Terminal care costs

Following progression on subsequent treatments, the model considers the costs of palliative care per month, sourced from NICE TA377 and inflated to the 2023/24 price year using data from the ONS.[25,30] The cost of palliative care per month in the analysis is £676.80. This aligns with the approach in TA951.

Costs for death are applied as a one-off cost to each death event in the model. The cost of death was sourced from NICE TA377 and inflated to the 2023/24 price year using data from the ONS.[25,30] The death cost applied in the analysis is £5,048.50. This aligns with the approach in TA951.

2.4.4.3 Genetic testing

As talazoparib with enzalutamide is licensed for all eligible adult patients with mCRPC in whom chemotherapy is not clinically indicated, regardless of biomarker status, no specific genetic testing is required and associated costs have not been included in the model.

2.5 *Uncertainty*

While there is always some uncertainty in economic models for HTA, the company considers the uncertainty in this model to be minimised by the use of data and assumptions that are aligned to the EAG and committee preference in TA951,including parametric extrapolation curves for rPFS and OS, and subsequent treatments.[19]

Uncertainty in the model results were explored through extensive deterministic sensitivity analysis (DSA), PSA, and scenario analyses. In the DSA, each variable was systematically increased and decreased based on 95% confidence intervals or published ranges. In the absence of data, the standard error was assumed to be 20%. In the PSA, values were drawn at random for each variable from its uncertainty distribution (see **Section 2.8** for further information).

2.6 *Summary of base case analysis inputs and assumptions*

2.6.1 Summary of base case analysis inputs

A summary of the parameters used in the economic model is provided in **Table** 34.

Table 34: Summary of base case parameters used in the economic model

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Model settings			
Population	Adult patients with mCRPC in whom chemotherapy is not clinically indicated	N/A	**Section 2.1**
Perspective	Payer (UK NHS and PPS)	N/A	
Time horizon	30 years	Fixed	
Proportion males	100.0%	N/A	
Starting age in model (years)	70.6	Fixed	
Body surface area (m^2)	1.99	Fixed	
Average weight (kg)	82.54	Fixed	
Half-cycle correction	Yes	Fixed	
Discount rate (cost and outcomes)	3.5%	OWSA: ±1.5 percentage points 0% and 5% explored in scenario analyses	
Age-adjusted utilities	Included	Exclusion explored in scenario analysis	**Section 2.3**
Clinical parameters			
Efficacy			
Talazoparib with enzalutamide rPFS parametric distribution	Generalised gamma	Alternative distributions explored in scenario analyses	**Section 2.2**
Talazoparib with enzalutamide parametric distribution	Generalised gamma	Alternative distributions explored in scenario analyses	
Olaparib with abiraterone rPFS distribution	Generalised gamma	Alternative distributions explored in scenario analyses	
Olaparib with abiraterone OS distribution	Generalised gamma	Alternative distributions explored in scenario analyses	
Subsequent treatment basket distribution (%)			

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Docetaxel with prednisolone	50.0	PSA: SE: 10.0 (beta distribution)	**Section 2.4.4.1**
Cabazitaxel with prednisolone	29.1	PSA: SE: 5.8 (beta distribution)	
Carboplatin	3.5	PSA: SE: 0.7 (beta distribution)	
Radium-223 dichloride	17.5	PSA: SE: 3.5 (beta distribution)	
Subsequent treatment duration (months)			
Docetaxel with prednisolone	5.86	PSA: SE: 1.17 (gamma distribution)	**Section 2.4.4.1**
Cabazitaxel with prednisolone	5.06	PSA: SE: 1.01 (gamma distribution)	
Carboplatin	2.10	PSA SE: 0.41 (gamma distribution)	
Radium-223 dichloride	5.52	PSA: SE: 1.10 (gamma distribution)	
Probability of AEs – Talazoparib with enzalutamide			
Anaemia	[redacted]	PSA: Alpha: 179; Beta: 219 (Beta distribution)	**Section 2.3.5.1**
Leukopenia	[redacted]	PSA: Alpha: 24; Beta: 374 (Beta distribution)	
Neutropenia	[redacted]	PSA: Alpha: 72; Beta: 326 (Beta distribution)	
Thrombocytopenia	[redacted]	PSA: Alpha: 24; Beta: 374 (Beta distribution)	
Venous thromboembolic event	[redacted]	PSA: Alpha: 5; Beta: 393 (Beta distribution)	
Probability of AEs – Olaparib with abiraterone			
Anaemia	16.1%	PSA: Alpha: 64; Beta: 334 (Beta distribution)	**Section 2.3.5.1**
Leukopenia	0.0%	PSA: Alpha: 0; Beta: 398 (Beta distribution)*	
Neutropenia	4.8%	PSA: Alpha: 19; Beta: 379 (Beta distribution)	
Thrombocytopenia	0.0%	PSA: Alpha: 0; Beta: 398 (Beta distribution)*	
Venous thromboembolic event	7.8%	PSA: Alpha: 31; Beta: 367 (Beta distribution)	
Duration of AEs (days)			
All AEs	14	OWSA: ±10% variation PSA: 2.8 (Gamma distribution)	**Section 2.3.5.1**
AE disutility			
Anaemia	-0.020	OWSA: ±10% variation PSA: 0.004 (Beta distribution)	**Section 2.3.5.1**

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Leukopenia	-0.020	OWSA: ±10% variation PSA: 0.004 (Beta distribution)	
Neutropenia	-0.020	OWSA: ±10% variation PSA: 0.004 (Beta distribution)	
Thrombocytopenia	-0.066	OWSA: ±10% variation PSA: 0.013 (Beta distribution)	
Venous thromboembolic event	-0.051	OWSA: ±10% variation PSA: 0.010 (Beta distribution)	
Probability of SREs – Talazoparib with enzalutamide			
Spinal cord compression	[redacted]	PSA: Alpha: 21; Beta: 377 (beta distribution)	**Section 2.3.5.2**
Radiation to bone	[redacted]	PSA: Alpha: 57; Beta: 341 (beta distribution)	
Surgery to bone	[redacted]	PSA: Alpha: 13; Beta: 385 (beta distribution)	
Pathologic bone fracture	[redacted]	PSA: Alpha: 23; Beta: 375 (beta distribution)	
Probability of SREs – Olaparib with abiraterone			
Spinal cord compression	15.5%	PSA: SE: 3.1% (beta distribution)	**Section 2.3.5.2**
Radiation to bone	67.7%	PSA: SE: 13.5% (beta distribution)	
Surgery to bone	4.1%	PSA: SE: 0.8% (beta distribution)	
Pathologic bone fracture	12.9%	PSA: SE: 2.6% (beta distribution)	
Duration of SREs (days)			
All SREs	30.44	OWSA: ±10% variation PSA: 6.09 (gamma distribution)	**Section 2.3.5.2**
SRE disutility			
Spinal cord compression	-0.555	OWSA: ±10% variation PSA: 0.111 (beta distribution)	**Section 2.3.5.2**
Radiation to bone	-0.070	OWSA: ±10% variation PSA: 0.014 (beta distribution)	
Surgery to bone	-0.130	OWSA: ±10% variation PSA: 0.026 (beta distribution)	
Pathologic bone fracture	-0.130	OWSA: ±10% variation PSA: 0.026 (beta distribution)	
Talazoparib with enzalutamide disease monitoring			
First three months: Proportion of patients requiring an office visit (consultant led)	50%	Fixed	**Section 2.4.2**
First three months: Proportion of patients	50%	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
requiring an office visit (nurse led)			
First three months: Proportion of patients requiring a CT scan	100%	Fixed	
First three months: Proportion of patients requiring a bone scan	20%	Fixed	
First three months: Proportion of patients requiring a complete blood count	100%	Fixed	
First three months: Proportion of patients requiring a liver function test	0%	Fixed	
First three months: Proportion of patients requiring a kidney function test	0%	Fixed	
First three months: Proportion of patients requiring treatment toxicity monitoring	0%	Fixed	
First three months: Proportion of patients requiring a prostate specific antigen test	100%	Fixed	
First three months: Frequency of office visits (consultant led)	2.175	Fixed	
First three months: Frequency of office visits (nurse led)	2.175	Fixed	
First three months: Frequency of CT scans	2.175	Fixed	
First three months: Frequency of bone scans	0.348	Fixed	
First three months: Frequency of complete blood counts	1.000	Fixed	
First three months: Frequency of liver function tests	0.000	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
First three months: Frequency of kidney function tests	0.000	Fixed	
First three months: Frequency of treatment toxicity monitoring	0.000	Fixed	
First three months: Frequency of prostate specific antigen test	2.175	Fixed	
Four plus months: Proportion of patients requiring an office visit (consultant led)	50%	Fixed	
Four plus months: Proportion of patients requiring an office visit (nurse led)	50%	Fixed	
Four plus months: Proportion of patients requiring a CT scan	100%	Fixed	
Four plus months: Proportion of patients requiring bone scan	20%	Fixed	
Four plus months: Proportion of patients requiring a complete blood count	100%	Fixed	
Four plus months: Proportion of patients requiring a liver function test	0%	Fixed	
Four plus months: Proportion of patients requiring a kidney function test	0%	Fixed	
Four plus months: Proportion of patients requiring treatment toxicity monitoring	0%	Fixed	
Four plus months: Proportion of patients requiring a prostate specific antigen test	100%	Fixed	
Four plus months: Frequency of office visits (consultant led)	1.088	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Four plus months: Frequency of office visits (nurse led)	1.088	Fixed	
Four plus months: Frequency of CT scans	2.175	Fixed	
Four plus months: Frequency of bone scans	0.348	Fixed	
Four plus months: Frequency of complete blood counts	1.000	Fixed	
Four plus months: Frequency of liver function tests	0.000	Fixed	
Four plus months: Frequency of kidney function tests	0.000	Fixed	
Four plus months: Frequency of treatment toxicity monitoring	0.000	Fixed	
Four plus months: Frequency of prostate specific antigen test	1.088	Fixed	
Olaparib with abiraterone disease monitoring			
First three months: Proportion of patients requiring an office visit (consultant led)	50%	Fixed	**Section 2.4.2**
First three months: Proportion of patients requiring an office visit (nurse led)	50%	Fixed	
First three months: Proportion of patients requiring a CT scan	100%	Fixed	
First three months: Proportion of patients requiring a bone scan	20%	Fixed	
First three months: Proportion of patients requiring a complete blood count	100%	Fixed	
First three months: Proportion of patients requiring a liver function test	100%	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
First three months: Proportion of patients requiring a kidney function test	100%	Fixed	
First three months: Proportion of patients requiring treatment toxicity monitoring	100%	Fixed	
First three months: Proportion of patients requiring a prostate specific antigen test	100%	Fixed	
First three months: Frequency of office visits (consultant led)	2.175	Fixed	
First three months: Frequency of office visits (nurse led)	2.175	Fixed	
First three months: Frequency of CT scans	2.175	Fixed	
First three months: Frequency of bone scans	0.348	Fixed	
First three months: Frequency of complete blood counts	2.175	Fixed	
First three months: Frequency of liver function tests	2.175	Fixed	
First three months: Frequency of kidney function tests	2.175	Fixed	
First three months: Frequency of treatment toxicity monitoring	1.001	Fixed	
First three months: Frequency of prostate specific antigen test	2.175	Fixed	
Four plus months: Proportion of patients requiring an office visit (consultant led)	50%	Fixed	
Four plus months: Proportion of patients requiring an office visit (nurse led)	50%	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Four plus months: Proportion of patients requiring a CT scan	100%	Fixed	
Four plus months: Proportion of patients requiring a bone scan	20%	Fixed	
Four plus months: Proportion of patients requiring a complete blood count	100%	Fixed	
Four plus months: Proportion of patients requiring a liver function test	100%	Fixed	
Four plus months: Proportion of patients requiring a kidney function test	100%	Fixed	
Four plus months: Proportion of patients requiring treatment toxicity monitoring	100%	Fixed	
Four plus months: Proportion of patients requiring a prostate specific antigen test	100%	Fixed	
Four plus months: Frequency of office visits (consultant led)	1.088	Fixed	
Four plus months: Frequency of office visits (nurse led)	1.088	Fixed	
Four plus months: Frequency of CT scans	2.175	Fixed	
Four plus months: Frequency of bone scans	0.348	Fixed	
Four plus months: Frequency of complete blood counts	1.088	Fixed	
Four plus months: Frequency of liver function tests	1.088	Fixed	
Four plus months: Frequency of kidney function tests	1.088	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Four plus months: Frequency of treatment toxicity monitoring	1.001	Fixed	
Four plus months: Frequency of prostate specific antigen test	1.088	Fixed	
First-line drug monitoring frequency			
At treatment initiation: Complete blood count	1.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	**Section 2.4.2**
At treatment initiation: Serum potassium assay test	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
At treatment initiation: Hepatic function panel	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
At treatment initiation: Office visit	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
At treatment initiation: Electrocardiogram	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
During treatment: Complete blood count	1.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
During treatment: Serum potassium assay test	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
During treatment: Hepatic function panel	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
During treatment: Office visit	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
During treatment: Electrocardiogram	0.000	Fixed for TALA+ENZA	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
		For OLA+ABI, varied in scenario analysis to drug specific SmPC	
Subsequent months: Complete blood count	1.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
Subsequent months: Serum potassium assay test	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
Subsequent months: Hepatic function panel	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
Subsequent months: Office visit	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
Subsequent months: Electrocardiogram	0.000	Fixed for TALA+ENZA For OLA+ABI, varied in scenario analysis to drug specific SmPC	
Second-line drug monitoring frequencies			
Docetaxel: Complete blood count	1.449	Fixed	**Section 2.4.4.1**
Docetaxel: Serum potassium assay test	0.000	Fixed	
Docetaxel: Hepatic function panel	0.000	Fixed	
Docetaxel: Office visit	0.000	Fixed	
Docetaxel: Electrocardiogram	0.333	Fixed	
Cabazitaxel, first month of treatment: Complete blood count	4.348	Fixed	
Cabazitaxel, first month of treatment: Serum potassium assay test	0.000	Fixed	
Cabazitaxel, first month of treatment: Hepatic function panel	0.000	Fixed	
Cabazitaxel, first month of treatment: Office visit	0.000	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Cabazitaxel, first month of treatment: Electrocardiogram	0.000	Fixed	
Cabazitaxel, during treatment: Complete blood count	1.449	Fixed	
Cabazitaxel, during treatment: Serum potassium assay test	0.000	Fixed	
Cabazitaxel, during treatment: Hepatic function panel	0.000	Fixed	
Cabazitaxel, during treatment: Office visit	0.000	Fixed	
Cabazitaxel, during treatment: Electrocardiogram	0.000	Fixed	
Radium-223, at treatment initiation: Complete blood count	1.000	Fixed	
Radium-223, at treatment initiation: Serum potassium assay test	0.000	Fixed	
Radium-223, at treatment initiation: Hepatic function panel	0.000	Fixed	
Radium-223, at treatment initiation: Office visit	0.000	Fixed	
Radium-223, at treatment initiation: Electrocardiogram	0.000	Fixed	
Radium-223, during treatment: Complete blood count	1.100	Fixed	
Radium-223, during treatment: Serum potassium assay test	0.000	Fixed	
Radium-223, during treatment: Hepatic function panel	0.000	Fixed	
Radium-223, during treatment: Office visit	0.000	Fixed	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Radium-223, during treatment: Electrocardiogram	0.000	Fixed	
Carboplatin: Complete blood count	4.348	Fixed	
Carboplatin: Serum potassium assay test	2.174	Fixed	
Carboplatin: Hepatic function panel	2.174	Fixed	
Carboplatin: Office visit	0.000	Fixed	
Carboplatin: Electrocardiogram	0.000	Fixed	
Utilities			
rPFS utility weight based on pooled data for both treatment arms of TALAPRO-2	[redacted]	OWSA: 95% CI: [redacted] PSA: SE: [redacted] (beta distribution)	**Section 2.3.6**
Utility while receiving subsequent treatment	0.658	OWSA: 95% CI: 0.574; 0.741 PSA: SE: 0.007 (beta distribution)	
Utility while receiving palliative care (NICE TA377)[25]	0.500	OWSA: 95% CI: 0.344; 0.656 PSA: SE: 0.080 (beta distribution)	
Cost parameters			
Wastage			
Consider wastage	Yes	Excluding wastage explored in scenario analyses	**Section 2.4.1.2**
Talazoparib with enzalutamide cost			
Talazoparib 0.25 mg: Price per package (£)	1,655	Fixed	**Section 2.4.1.1**
Talazoparib: Discount	[redacted]	PSA: SE: 16.7% (beta distribution)	
Talazoparib: Percentage of intended dose received	100%	Fixed*	
Enzalutamide: Price per package (£)	2,735	OWSA: ±10% variation	
Enzalutamide: Discount	0%	Fixed*	
Enzalutamide: Percentage of intended dose received	100%	Fixed*	
Olaparib with abiraterone cost			
Olaparib 150 mg: Price per package (£)	2,318	OWSA: ±10% variation	**Section 2.4.1.1**

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Olaparib: Discount	0%	Fixed*	
Olaparib: Percentage of intended dose received	100%	Fixed*	
Abiraterone acetate: Price per package (£)	77	OWSA: ±10% variation	
Abiraterone acetate: Percentage of intended dose received	100%	Fixed*	
Prednisolone: Price per package (£)	0.41	OWSA: ±10% variation	
Subsequent treatment cost			
Docetaxel: Price per package (£)	4.49	OWSA: ±10% variation	**Section 2.4.4.1**
Docetaxel: Percentage of intended dose received	100%	Fixed*	
Docetaxel: Premedication cost per administration (£)	4.32	PSA: SE: 0.86 (gamma distribution)	
Docetaxel: Drug administration cost per administration	201.66	PSA: SE: 40.33 (gamma distribution)	
Cabazitaxel: Price per package (£)	3,696	OWSA: ±10% variation	
Cabazitaxel: Discount	0%	Fixed*	
Cabazitaxel: Percentage of intended dose received	100%	Fixed*	
Cabazitaxel: Premedication cost per administration (£)	100.66	PSA: SE: 20.13 (gamma distribution)	
Cabazitaxel: Drug administration cost per administration	201.66	PSA: SE: 40.33 (gamma distribution)	
Radium-223: Price per package (£)	5,302	OWSA: ±10% variation	
Radium-223: Discount	0%	Fixed*	
Radium-223: Percentage of intended dose received	100%	Fixed*	
Radium-223: Drug administration cost per administration	201.66	PSA: SE: 40.33 (gamma distribution)	

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Carboplatin: Price per package (£) – 600mg	38.93	OWSA: ±10% variation	
Carboplatin: Price per package (£) – 450mg	23.18	OWSA: ±10% variation	
Carboplatin: Price per package (£) – 150mg	12.18	OWSA: ±10% variation	
Carboplatin: Price per package (£) – 50mg	6.71	OWSA: ±10% variation	
Carboplatin: Discount	0%	Fixed*	
Carboplatin: Percentage of intended dose received	100%	Fixed*	
Carboplatin: Drug administration cost per administration	201.66	PSA: SE: 40.33 (gamma distribution)	
AE cost (£)			
Anaemia	649.79	OWSA: ±10% variation PSA: 129.96 (Gamma distribution)	**Section 2.3.5.1**
Leukopenia	193.89	OWSA: ±10% variation PSA: 38.78 (Gamma distribution)	
Neutropenia	193.89	OWSA: ±10% variation PSA: 38.78 (Gamma distribution)	
Thrombocytopenia	193.89	OWSA: ±10% variation PSA: 38.78 (Gamma distribution)	
Venous thromboembolic event	193.89	OWSA: ±10% variation PSA: 38.78 (Gamma distribution)	
SRE cost (£)			
Spinal cord compression	7,848.26	OWSA: ±10% variation PSA: 1569.65 (Gamma distribution)	**Section 2.3.5.2**
Radiation to bone	1,015.04	OWSA: ±10% variation PSA: 203.01 (Gamma distribution)	
Surgery to bone	5,140.57	OWSA: ±10% variation PSA: 1028.11 (Gamma distribution)	
Pathologic bone fracture	6,294.00	OWSA: ±10% variation PSA: 1258.80 (Gamma distribution)	
Disease and drug monitoring cost (£)			

Parameter	Value	Measurement of uncertainty and distribution: Confidence interval (distribution)	Reference to section in submission
Office visit (consultant led)	193.89	PSA: SE: 38.78 (gamma distribution)	Section 2.4.2
Office visit (nurse led)	49.33	PSA: SE: 9.87 (gamma distribution)	
CT scan	121.39	PSA: SE: 24.28 (gamma distribution)	
Bone scan	271.55	PSA: SE: 54.31 (gamma distribution)	
Complete blood count	3.10	PSA: SE: 0.62 (gamma distribution)	
Liver function test	1.53	PSA: SE: 0.31 (gamma distribution)	
Kidney function test	3.10	PSA: SE: 0.62 (gamma distribution)	
Treatment toxicity monitoring	3.10	PSA: SE: 0.62 (gamma distribution)	
Prostate specific antigen test	1.53	PSA: SE: 0.31 (gamma distribution)	
Serum potassium assay test	3.10	PSA: SE: 0.62 (gamma distribution)	
Hepatic function panel	1.53	PSA: SE: 0.31 (gamma distribution)	
Electrocardiogram	641.76	PSA: SE: 128.35 (gamma distribution)	
Palliative care and death (£)			
Palliative care cost per month	676.80	OWSA: ±10% PSA: 135.36 (gamma distribution)	Section 2.4.4.2
Death (one-time cost)	5,048.50	OWSA: ±10% PSA: 1,009.70 (gamma distribution)	

*Values of 0% and 100% are not varied in the PSA.
Abbreviations: AE – Adverse event; CI – Confidence interval; CT – Computed tomography; FE – Fixed effect; kg – Kilogram; m – Meter; MAIC – Matching-adjusted indirect comparison; mCRPC – Metastatic castration-resistant prostate cancer; mg – Miligram; N/A – Not applicable; NHS – National Health Service; NICE – National Institute of Health and Care Excellence; OS – Overall survival; OWSA – One-way sensitivity analysis; PD – Progressed disease; PPS – Personal Social Services; PSA – Probabilistic sensitivity analysis; RE – Random effect; rPFS – Radiographic progression-free survival; SE – Standard error; SRE – Skeletal-related event; TTD – Time-to-treatment discontinuation; UK – United Kingdom

2.6.2 Assumptions

A summary of the key assumptions in the base case model is provided in **Table 35**.

Table 35: Summary of key model assumptions

Aspect	Assumption	Justification
Survival curves	Independent models are fitted for rPFS and OS for both treatment arms. Talazoparib with enzalutamide: Parametric survival curves were fitted to weighted KMs generated from the MAIC of TALAPRO-2 vs PROpel. Olaparib with abiraterone: Parametric survival curves were fitted to unadjusted KMs from PROpel.	In line with the EAG's concern with PH, independent models (all using generalised gamma in line with TA951[19]) capture different shapes of the hazards between the two arms. Using TALAPRO-2 patient-level data provides the highest level of accuracy for talazoparib with enzalutamide.
Time-to-treatment discontinuation	Time-to-treatment discontinuation is set equal to rPFS.	Due to the unavailability of time-to-treatment discontinuation data prior to submission, a conservative assumption is made.
Mortality	If OS mortality hazard falls below the male general population mortality hazard, the OS mortality hazard is set equal to the age-matched male general population mortality hazard.	Clinically plausible assumption that patients with mCRPC have at least the same risk of mortality as the age-matched male population.
Subsequent treatment	The subsequent treatment market shares are informed by TA951 and assumed to be the same for the talazoparib with enzalutamide arm and the olaparib with abiraterone arm.	Consistent with TA951.[19]
PD health state	The PD health state is split into two, with separate utility values: PD on subsequent treatment, and PD in palliative care (i.e., following progression on subsequent treatment).	Consistent with TA377.[25]

Aspect	Assumption	Justification
Safety	Only Grade 3+ AEs occurring in ≥5% patients are included.	Grade ≥3 AEs are considered to have the most significant impact on patient quality of life and NHS resources. This is consistent with TA951.[19]
Monitoring	Drug monitoring requirements for olaparib with abiraterone and subsequent treatments were assumed to be equivalent to the requirements for talazoparib with enzalutamide.	As per the EAG base case in the cost-comparison submission. This is a conservative assumption as clinical expert opinion received by the EAG was that although long-term monitoring requirements would be the same for both treatments, abiraterone monitoring would be higher than other treatments in the first 12 weeks of treatment.
	For combination regimens, drug monitoring continues for the duration of treatment of the entire regimen even if patients discontinue one drug before the other.	The continued drug monitoring of both treatments in a combination regimen despite the discontinuation of one drug is a conservative estimate that aims to capture potential complications associated with combination regimens.
Utilities	Utility values vary by health state but not by treatment arm.	Consistent with TA951.[19]
	Age-adjusted utility decrements are modelled.	To capture the decrease in HRQoL with age.
End-of-life care cost	A one-off cost (from TA377) is applied when patients progress into the death state.	Consistent with TA951, TA391, and TA377.[19, 25,52]

Abbreviations: AE – Adverse event; HRQoL – Health-related quality of life; mCRPC – Metastatic castration-resistant prostate cancer; NHA – New hormonal agent; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; OS – Overall survival; PARPi – Poly adenosine diphosphate ribose polymerase inhibitor; PD – Progressed disease; PSM – Partitioned survival model; PSS – Personal Social Services; rPFS – Radiographic progression-free survival; TA – Technology appraisal

2.7 *Base case results*

2.7.1 Base case incremental cost-effectiveness analysis results

When applying a PAS discount of [redacted] to talazoparib, the deterministic base case results show that talazoparib with enzalutamide is associated with [redacted] incremental QALYs at an incremental cost of [redacted], which translates to a [redacted] ICER compared to olaparib with abiraterone over a 30-year time horizon, and a net monetary benefit of [redacted] (**Table 36**).

Table 36: Base case deterministic results

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; mCRPC – Metastatic castration-resistant prostate cancer; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

2.8 *Exploring uncertainty*

2.8.1 Probabilistic sensitivity analysis

PSA was conducted to assess the impact of parameter uncertainty on the results of the analysis in the model base case; 5,000 simulations were performed, and for each simulation, a value was drawn at random for each variable from its uncertainty distribution

simultaneously, and the resulting costs, outcomes, and incremental results were recorded. 5,000 iterations were considered sufficient to test uncertainty based on an assessment of convergence and Monte Carlo Error.

The results of the base case PSA are presented in **Table 37**, with an incremental cost-effectiveness plane (ICEP) and cost-effectiveness acceptability curve (CEAC) presented in **Figure 15** and **Figure 16**, respectively.

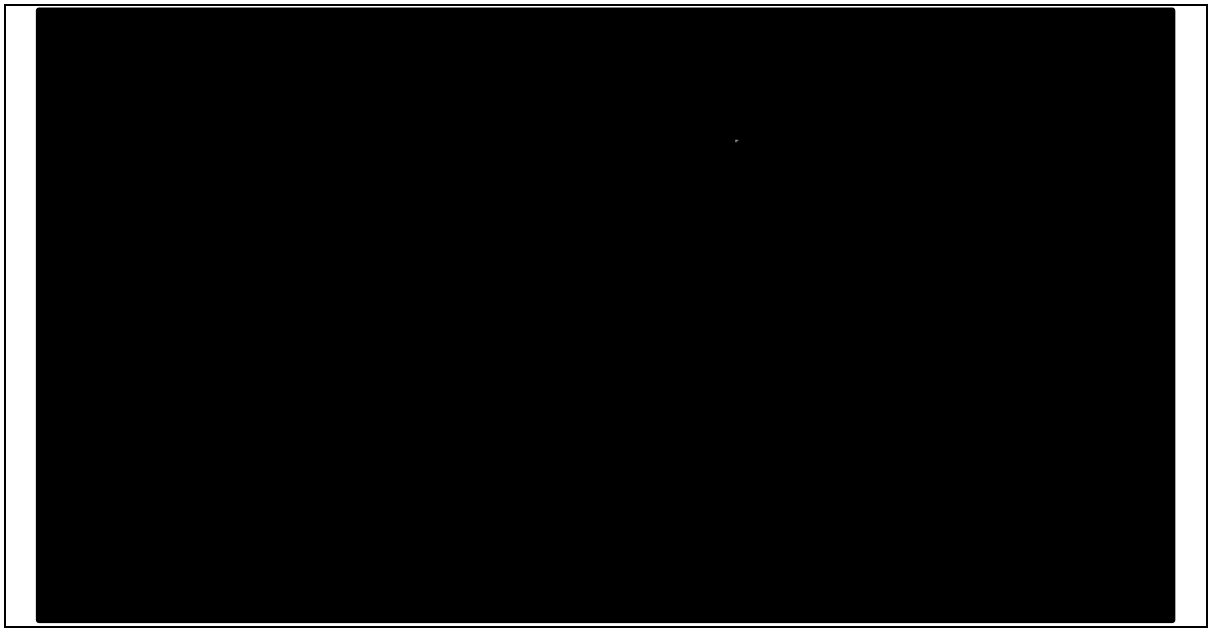
Based on the PSA, treatment with talazoparib with enzalutamide in patients with mCRPC was associated with incremental costs and QALYs of [redacted] and [redacted], respectively, with a corresponding [redacted] ICER compared to olaparib with abiraterone. The mean probabilistic results [redacted] to the deterministic results, indicating that the model is robust to parameter uncertainty.

Table 37: PSA base case results

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

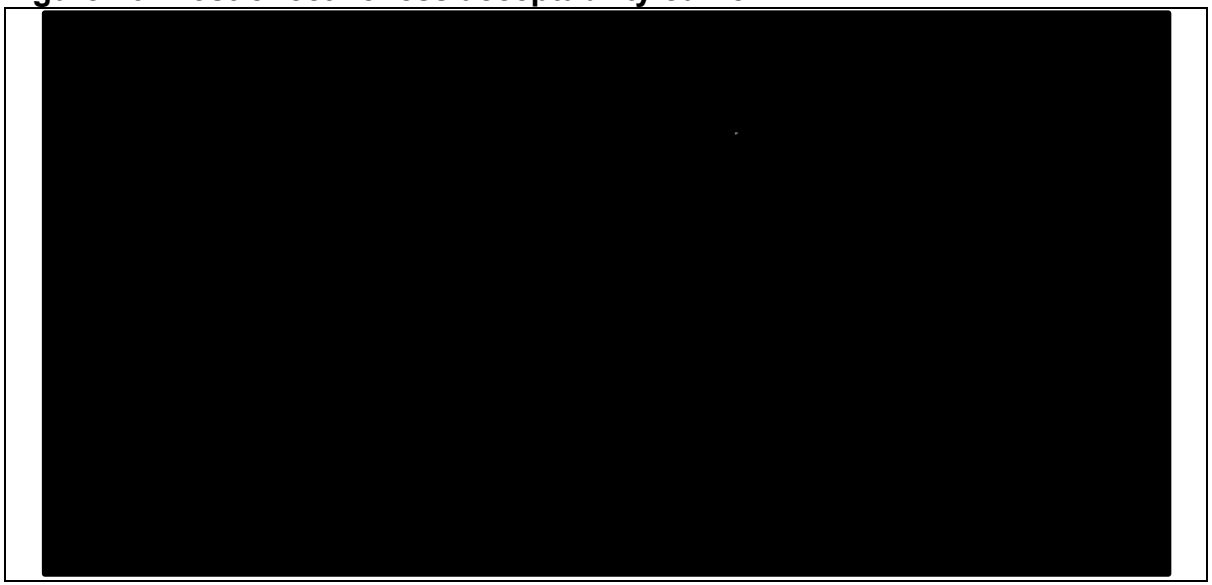
Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; mCRPC – Metastatic castration-resistant prostate cancer; NMB – Net monetary benefit; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years

Figure 15: Incremental cost-effectiveness plane



Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; OLA – Olaparib; TALA - Talazoparib

Figure 16: Cost-effectiveness acceptability curve



Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; OLA – Olaparib; TALA - Talazoparib

2.8.2 One-way sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted by varying one parameter at a time and assessing the subsequent impact on cost-effectiveness. By adjusting each parameter individually, the sensitivity of the model results to that parameter can be assessed.

The OWSA was conducting by allocating a 'low' and a 'high' value to each parameter based on the lower bound and upper bound of the parameter's 95% confidence interval. In the absence of confidence interval data, the variable was altered by +/- 10%.

An OWSA tornado diagram presenting the top ten most sensitive parameters is presented in **Figure 17**, with tabulated results presented in

Table 38. The parameters with the biggest impact on the ICER are [redacted]

Figure 17: OWSA tornado diagram

Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; OLA – Olaparib; PD – Progressed disease; rPFS – Radiographic progression-free survival; SRE – Skeletal-related event; TALA – Talazoparib

Table 38: Tabulated OWSA results for talazoparib with enzalutamide versus olaparib with abiraterone

Parameter	Lower bound NMB	Upper bound NMB	Difference
PD while receiving palliative care utility weight	[redacted]	[redacted]	[redacted]
Discount rate for costs (%/year)	[redacted]	[redacted]	[redacted]
OLA + ABI: Weighted average cost of second-line treatment	[redacted]	[redacted]	[redacted]
Discount rate for health outcomes (%/year)	[redacted]	[redacted]	[redacted]
Palliative care cost per month	[redacted]	[redacted]	[redacted]
PD while receiving second-line treatment utility weight	[redacted]	[redacted]	[redacted]
TALA + ENZA: Weighted average cost of second-line treatment	[redacted]	[redacted]	[redacted]
rPFS utility weight: Utility based on pooled data for both treatment arms of TALAPRO-2	[redacted]	[redacted]	[redacted]
SRE one-time cost: Spinal cord compression	[redacted]	[redacted]	[redacted]
SRE one-time cost: Radiation to bone	[redacted]	[redacted]	[redacted]
SRE one-time cost: Pathologic bone fractures	[redacted]	[redacted]	[redacted]
SRE - Spinal Cord Compression: Disutility	[redacted]	[redacted]	[redacted]
SRE - Radiation to bone: Duration (days)	[redacted]	[redacted]	[redacted]
Total disease monitoring cost per month during 2L treatment	[redacted]	[redacted]	[redacted]
SRE one-time cost: Surgery to bone	[redacted]	[redacted]	[redacted]
Death (one-time cost)	[redacted]	[redacted]	[redacted]
SRE - Pathological bone fractures: Disutility	[redacted]	[redacted]	[redacted]
SRE - Pathological bone fractures: Duration (days)	[redacted]	[redacted]	[redacted]
AE one-time cost: Neutropenia	[redacted]	[redacted]	[redacted]
AE one-time cost: Venous Thromboembolic Event	[redacted]	[redacted]	[redacted]
AE one-time cost: Leukopenia	[redacted]	[redacted]	[redacted]
AE one-time cost: Thrombocytopenia	[redacted]	[redacted]	[redacted]
AE: Anaemia: Disutility	[redacted]	[redacted]	[redacted]
AE: Anaemia: Duration (days)	[redacted]	[redacted]	[redacted]
AE: Thrombocytopenia: Disutility	[redacted]	[redacted]	[redacted]
AE: Thrombocytopenia: Duration (days)	[redacted]	[redacted]	[redacted]

Parameter	Lower bound NMB	Upper bound NMB	Difference
SRE - Surgery to bone: Disutility	[redacted]	[redacted]	[redacted]
SRE - Surgery to bone: Duration (days)	[redacted]	[redacted]	[redacted]
AE: Venous Thromboembolic Event: Disutility	[redacted]	[redacted]	[redacted]
AE: Venous Thromboembolic Event: Duration (days)	[redacted]	[redacted]	[redacted]
AE: Neutropenia: Disutility	[redacted]	[redacted]	[redacted]
AE: Neutropenia: Duration (days)	[redacted]	[redacted]	[redacted]
AE: Leukopenia: Disutility	[redacted]	[redacted]	[redacted]
AE: Leukopenia: Duration (days)	[redacted]	[redacted]	[redacted]
Enzalutamide: Price per package	[redacted]	[redacted]	[redacted]
Olaparib 150 mg: Price per package	[redacted]	[redacted]	[redacted]
Abiraterone acetate: Price per package	[redacted]	[redacted]	[redacted]
Prednisolone: Price per package	[redacted]	[redacted]	[redacted]
2L Docetaxel: Price per package	[redacted]	[redacted]	[redacted]
Cabazitaxel: Price per package	[redacted]	[redacted]	[redacted]
Radium-223 dichloride: Price per package	[redacted]	[redacted]	[redacted]
2L Carboplatin: Price per package (600mg)	[redacted]	[redacted]	[redacted]
2L Carboplatin: Price per package (450mg)	[redacted]	[redacted]	[redacted]
2L Carboplatin: Price per package (150mg)	[redacted]	[redacted]	[redacted]
2L Carboplatin: Price per package (50mg)	[redacted]	[redacted]	[redacted]

Abbreviations: ABI – Abiraterone; AE – Adverse event; ENZA – Enzalutamide; ICER – Incremental cost-effectiveness ratio; OLA – Olaparib; OWSA – One-way sensitivity analysis; PD – Progressed disease; rPFS – Radiographic progression-free survival; SRE – Skeletal-related event; TALA – Talazoparib

2.8.3 Scenario analysis

Scenario analyses were performed to test underlying model assumptions and the use of alternative input parameters. The list of scenarios explored is presented in **Table 39**. The deterministic scenario analysis results for talazoparib with enzalutamide versus olaparib with abiraterone are presented in **Table 40**. [redacted]

Table 39: Summary of scenario analyses

ID	Category	Base case value	Scenario value	Rationale
Discount_0	Discount rate	3.5%	0%	To explore the impact of discounting
Discount_5			5%	
rPFS_5	Talazoparib with enzalutamide rPFS	Generalised gamma distribution	Log-logistic distribution	To explore the impact of alternative rPFS distributions for talazoparib with enzalutamide
rPFS_6			Log-normal distribution	
OS_5	Talazoparib with enzalutamide OS	Generalised gamma distribution	Log-logistic distribution	To explore the impact of alternative OS distributions for talazoparib with enzalutamide
OS_6			Log-normal distribution	
Wastage_2	Wastage	Consider wastage	Do not consider wastage	To explore the impact of not considering drug wastage
Age_adjusted_no	Age-adjusted utilities	Applied	Not applied	To explore the impact of not applying age-adjustment to utilities
Drug_monitoring_drugspecific	Drug monitoring frequency	OLA+ABI drug monitoring requirements equal to TALA+ENZA monitoring requirements	OLA+ABI SmPC	To explore the impact of adopting drug-specific monitoring requirements for OLA+ABI
	Disease monitoring frequency	Drug-specific disease monitoring requirements	OLA+ABI disease monitoring requirements equal to TALA+ENZA monitoring requirements	To explore the impact of adopting equal disease monitoring requirements for both treatments

Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; MAIC – Matching-adjusted indirect comparison; OLA – Olaparib; OS – Overall survival; RDI – Relative dose intensity; rPFS – Radiographic progression-free survival; SmPC – Summary of product characteristics; TALA – Talazoparib; th – Time horizon; TTD – Time-to-discontinuation

Table 40: Summary of the deterministic scenario analyses results for talazoparib with enzalutamide versus olaparib with abiraterone

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER per QALY (£)
Base case	[redacted]	[redacted]	[redacted]
TALAPRO-2 OS: log-logistic distribution	[redacted]	[redacted]	[redacted]
TALAPRO-2 rPFS: log-logistic distribution	[redacted]	[redacted]	[redacted]
Drug monitoring frequency source: TALA+ENZA and OLA+ABI SmPCs	[redacted]	[redacted]	[redacted]
TALAPRO-2 OS: log-normal distribution	[redacted]	[redacted]	[redacted]
TALAPRO-2 rPFS: log-normal distribution	[redacted]	[redacted]	[redacted]
Discount rate for costs and health outcomes (%/year): 5	[redacted]	[redacted]	[redacted]
OLA+ABI disease monitoring frequency equal to TALA+ENZA	[redacted]	[redacted]	[redacted]
Age-adjusted utilities not applied	[redacted]	[redacted]	[redacted]
Consider wastage? No	[redacted]	[redacted]	[redacted]
Discount rate for costs and health outcomes (%/year): 0	[redacted]	[redacted]	[redacted]

Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; ICER – Incremental cost-effectiveness ratio; OLA – Olaparib; OS – Overall survival; rPFS – Radiographic progression-free survival; SmPC – Summary of product characteristics; TALA – Talazoparib

2.9 *Subgroup analysis*

No subgroup analyses were conducted.

2.10 *Validation*

2.10.1 Validation of cost-effectiveness analysis

2.10.1.1 Internal validation

Upon completion of the model programming, a rigorous and comprehensive quality check of the model was conducted by an internal senior health economist not involved with the original programming to ensure the completed model contained no errors and worked as intended. This included validating the logical structure of the model, the expressions and sequences of calculations, and the values of numbers used as model inputs.

An extreme-value sensitivity analysis was also conducted on all applicable model inputs. Whilst conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the results included in this report.

2.10.1.2 External validation

An external expert in health technology assessment submissions was consulted during the development of the core CEM. All suggestions made by the expert that pertained to model structure and assumptions, among other topics, were implemented.

2.11 *Interpretation and conclusions of economic evidence*

A CUA was developed for the economic evaluation of talazoparib with enzalutamide versus olaparib with abiraterone. In the base case analysis, talazoparib with enzalutamide was associated with [redacted] incremental QALYs and [redacted] incremental costs compared to olaparib with abiraterone. The corresponding ICER was [redacted]. The base

case provides a [redacted] of talazoparib with enzalutamide, with potential benefits in safety, HRQoL, and resource use not captured in the analysis.

The base case results are [redacted]. Testing the sensitivity of the model results towards individual parameter changes demonstrated [redacted] in the parameters included in the model.

We acknowledge the cost-effectiveness results presented in this addendum do not consider commercially confidential patient access scheme (PAS) discounts for olaparib, enzalutamide and subsequent treatments, however, we believe both the deterministic and probabilistic base case ICERs for talazoparib with enzalutamide [redacted] compared to olaparib with abiraterone when PAS discounts are applied.

References

1. Scottish Medicines Consortium. Talazoparib (Talzenna) Advice Document. 2025. at <https://scottishmedicines.org.uk/media/9019/talazoparib-talzenna-abb-final-feb-2025-for-website.pdf>

2. Pfizer. Clinical expert validation interview outcomes. (Data on file). 2024.

3. Pfizer. TALAPRO 2 CSR. (Data on file). 2024.

4. Pfizer. TALAPRO 2 CSR. (Data on file). 2022.

5. Agarwal N, Azad AA, Carles J, *et al.* Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet* 2023. 402: 291–303.

6. Pfizer. SLR technical report. 2024.

7. Pfizer. TALA+ENZA 1L mCRPC MAIC All-comers Survival Analyses. 2024.

8. Saad F, Clarke N, Oya M, *et al.* Olaparib plus abiraterone versus placebo plus abiraterone in metastatic castration-resistant prostate cancer (PROpel): final prespecified overall survival results of a randomised, double-blind, phase 3 trial. *The lancet Oncology* 2023. 24: 1094-1108.

9. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, *et al.* Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM evidence* 2022. 1: EVIDoa2200043.

10. Signorovitch JE, Sikirica V, Erder MH, *et al.* Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research. *Value in Health* 2012. 15: 940–947.

11. Phillippo DM, Dias S, Ades AE, *et al.* Assessing the performance of population adjustment methods for anchored indirect comparisons: A simulation study. *Statistics in Medicine* 2020. 39: 4885–4911.

12. Armstrong AJ, Lin P, Higano CS, *et al.* Development and validation of a prognostic model for overall survival in chemotherapy-naïve men with metastatic castration-resistant prostate cancer. *Annals of Oncology* 2018. 29: 2200–2207.

13. Phillippo DM, Ades AE, Dias S, *et al.* Methods for population-adjusted indirect comparisons in health technology appraisal. *Medical decision making* 2018. 38: 200–211.

14. Signorovitch JE, Wu EQ, Yu AP, *et al.* Comparative effectiveness without head-to-head trials: a method for matching-adjusted indirect comparisons applied to psoriasis treatment with adalimumab or etanercept. *Pharmacoeconomics* 2010. 28: 935–945.

15. Guyot P, Ades A, Ouwens MJ, *et al.* Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC medical research methodology* 2012. 12: 1–13.

16. Phillippo D, Ades T, Dias S, *et al.* NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.

17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in medicine* 2009. 28: 3083–3107.

18. NICE. NICE health technology evaluations: the manual. 2023. at <https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741>

19. NICE. NICE TA951: Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. 2024. at <https://www.nice.org.uk/guidance/ta951/resources/olaparib-with-abiraterone-for-untreated-hormonerelapsed-metastatic-prostate-cancer-pdf-82615723963333>

20. NICE. NICE TA580: Enzalutamide for treating nonmetastatic hormone-relapsed prostate cancer. 2018. at <https://www.nice.org.uk/guidance/ta580/documents/committee-papers>

21. NICE. NICE TA660: Darolutamide with androgen deprivation therapy for treating non-metastatic hormone-relapsed prostate cancer. 2020. at <https://www.nice.org.uk/guidance/ta660/evidence/committee-papers-pdf-8949137869>

22. NICE. NICE TA712: Enzalutamide with ADT for treating metastatic hormone-sensitive prostate cancer. 2019. at <https://www.nice.org.uk/guidance/ta712/evidence/committee-papers-pdf-9191003869>

23. NICE. NICE TA740: Apalutamide for treating non-metastatic hormone-relapsed prostate cancer and metastatic hormone-sensitive prostate cancer. 2021. at <https://www.nice.org.uk/guidance/ta740/evidence/appraisal-consultation-committee-papers-pdf-9266538637>

24. NICE. NICE TA741: Apalutamide for treating non-metastatic hormone-relapsed prostate cancer and metastatic hormone-sensitive prostate cancer. 2020. at <https://www.nice.org.uk/guidance/ta741/evidence/appraisal-consultation-committee-papers-pdf-9266538637>

25. NICE. NICE TA377: Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. 2016. at <https://www.nice.org.uk/guidance/ta377/documents/prostate-cancer-metastatic-hormonerelapsed-enzalutamide-id683-committee-papers-2>

26. NHS. National Schedule of NHS Costs (2023-2024). 2024. at <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>

27. Drugs A to Z | BNF content published by NICE. at <https://bnf.nice.org.uk/drugs/>

28. Drugs and pharmaceutical electronic market information tool (eMIT). *GOV.UK* 2024. at <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>

29. Jones, K., Weatherly, H., Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S., Premji, S., Teo, H. Unit Costs of Health and Social Care 2023. 2023. at <https://kar.kent.ac.uk/105685/1/The%20unit%20costs%20of%20health%20and%20social%20care_Final3.pdf>

30. CPI INDEX 06 : HEALTH 2015=100 - Office for National Statistics. at <https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bz/mm23>

31. NHS. National Schedule for NHS costs. 2021. at <https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/>

32. CPI INDEX 00: ALL ITEMS 2015=100 - Office for National Statistics. at <https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/d7bt/mm23>

33. Survival analysis TSD. 2024. at <https://www.sheffield.ac.uk/nice-dsu/tsds/survival-analysis>

34. Burnham KP & Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociological Methods & Research* 2004. 33: 261–304.

35. Table 17, Time to Treatment Discontinuation of Olaparib and Time to Treatment Discontinuation of Abiraterone. 2024. at <https://www.ncbi.nlm.nih.gov/books/NBK604445/table/tr8269868067031982_ch02_t17/>

36. ONS. National life tables: UK. 2024. at <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables>

37. Hernández Alava M, Pudney S & Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. *Pharmacoeconomics* 2023. 41: 199–207.

38. Diaby V, Adunlin G, Ali AA, *et al.* Cost-effectiveness analysis of 1st through 3rd line sequential targeted therapy in HER2-positive metastatic breast cancer in the United States. *Breast cancer research and treatment* 2016. 160: 187–196.

39. Pfizer. Final TP-2 Utility Analysis Report Draft. 2025.

40. EMC. Lynparza 100mg Film-Coated Tablets SmPC. 2024. at <https://www.medicines.org.uk/emc/product/9204/smpc/print>

41. EMC. Talzenna SmPC. 2024. at <https://www.medicines.org.uk/emc/product/10734/smpc>

42. EMC. Xtandi 40 mg film coated tablets SmPC. 2024. at <https://www.medicines.org.uk/emc/product/10318/smpc/print>

43. EMA. Zytiga SmPC. 2022. at <https://www.ema.europa.eu/en/documents/product-information/zytiga-epar-product-information_en.pdf>

44. EMC. Docetaxel 20 mg/ml concentrate for solution for infusion SmPC. 2023. at <https://www.medicines.org.uk/emc/product/7206/smpc/print>

45. EMC. Cabazitaxel 60 mg Concentrate and Solvent For Solution For Infusion SmPC. 2024. at <https://www.medicines.org.uk/emc/product/12319/smpc/print>

46. EMC. Carboplatin 10 mg/ml Intravenous Infusion Latex containing Vial Stopper. 2024. at <https://www.medicines.org.uk/emc/product/3787/smpc/print>

47. EMC. Xofigo 1100 kBq/mL solution for injection SmPC. 2024. at <https://www.medicines.org.uk/emc/product/5204/smpc/print>

48. NICE. NICE TA412: Radium-223 dichloride for treating metastatic hormone-relapsed prostate cancer with bone metastases. 2016. at <https://www.nice.org.uk/guidance/ta412/documents/committee-papers>

49. Tannock IF, de Wit R, Berry WR, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004. 351: 1502–1512.

50. de Wit R, de Bono J, Sternberg CN, *et al.* Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. *N Engl J Med* 2019. 381: 2506–2518.

51. Pemberton L, Allen C, Handel E, *et al.* Carboplatin in Metastatic Castrate Resistant Prostate Cancer: A Retrospective Study of Heavily Pretreated Patients (COMPACT). *Clin Genitourin Cancer* 2024. 22: 580–585.

52. NICE. NICE TA391: Cabazitaxel for the second line treatment of hormone refractory, metastatic prostate cancer. 2011. at <https://www.nice.org.uk/guidance/ta391/documents/committee-papers-3>

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Summary of Information for Patients (SIP)

August 2024

File name	Version	Contains confidential information	Date
ID4004_Talazoparib_Summary_Information_Patients_19th August_[no CON]	Final	No	19th August 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: talazoparib Brand name: Talzenna®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Talazoparib in combination with enzalutamide is intended for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Talazoparib received a marketing authorisation from the European Medicines Agency (EMA) in 2019 for the treatment of adult patients with germline BRCA1/2 mutations who have HER2-negative locally advanced or metastatic breast cancer. In January 2024 the EMA agreed the expansion of the marketing authorisation to include the indication for talazoparib in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

No existing collaborations or conflicts of interests.

Pfizer had provided financial support to ORCHID to help support a disease awareness campaign in September 2023.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

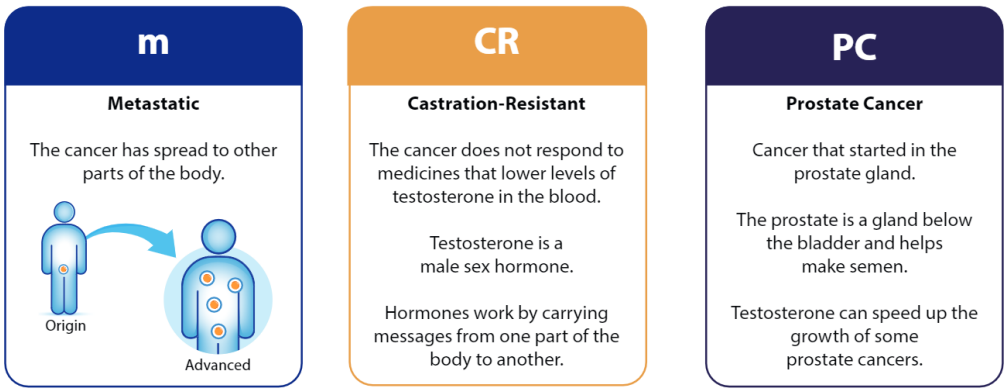
Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Main condition that the medicine plans to treat:

Prostate cancer develops when abnormal cells form and grow in the prostate gland. If prostate cancer spreads beyond the prostate, it is called "metastatic," where it is found growing in nearby organs or tissues. With metastatic CRPC (mCRPC), the cancer stops responding to hormone treatment. It can spread to nearby lymph nodes, bones, the bladder, rectum, liver, lungs, and maybe the brain.

Metastatic castration-resistant prostate cancer is known as mCRPC. mCRPC is a type of advanced prostate cancer.



Main symptoms of disease:

Initial signs and symptoms from mCRPC depend and vary based on the size of the tumours and the extent of spread of the cancer cells. Sometimes the patients might not experience any symptoms.

However, the symptomatic patients may begin with:

- Trouble urinating
- Pain
- Blood in urine
- Feeling more tired or weak than normal

- Weight loss
- Shortness of breath
- Bone pain

Burden of disease:

Prostate cancer is the most common and most frequently diagnosed form of cancer in men in the United Kingdom (UK). [2] There are approximately 55,100 new prostate cancer cases annually in the UK, of which 13% present with metastatic disease at diagnosis. Approximately 12,000 prostate cancer deaths are recorded annually in the UK, making prostate cancer the second most common cause of cancer death in males in the UK.[2,3]

Most patients develop mCRPC following progression from earlier stages of the disease, with approximately 65–73% progressing from metastatic castration-sensitive prostate cancer (mCSPC), and 26–35% progressing from non-metastatic castration-resistant prostate cancer (nmCRPC). In the UK, the estimated prevalence of mCRPC is 1.2% among overall prostate cancer cases, and the estimated incidence rate is approximately 78–85 per 100,000 population.[4]

Impact on patient:

Unlike localised prostate cancer, which has a positive prognosis with 5-year survival rates at 99.6%,26 the prognosis for mCRPC remains poor, with a 5-year survival rate for patients with metastases of 30%.[5,6]

Patients with mCRPC report a high symptom burden, including fatigue, pain, urinary frequency, and substantial health-related quality of life (HRQoL) decline. Additionally, patients with bone metastases experience considerable morbidity burden from skeletal-related events (SREs), which include pathological fractures (when force or impact does not cause the break to happen), spinal cord compression, severe pain requiring radiotherapy, or surgery. As mCRPC is incurable and has a poor prognosis, the main goal of treatment is to prolong survival and maintain quality of life for patients.[7–10]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

There is no national prostate cancer screening programme in the UK.

The first step of diagnosis involves a careful review of medical history as well as a physical examination. This entails an assessment of any reported symptoms alongside an evaluation of relevant risk factors. In addition, the doctor will perform a digital rectal examination (DRE).

If prostate cancer is suspected a Prostate-specific Antigen (PSA) blood test is done. This tests for the presence of a specific protein called the prostate-specific antigen. While all men have some PSA, higher levels may indicate the presence of cancer. Men >50 years can request a PSA test at any time from their GPs and for men with increased risk of prostate cancer, this test can be offered from the age 45 years. The PSA blood test is not definitive, but it can help doctors rule out cases where cancer is unlikely. Elevated PSA levels will indicate the need for further tests.

Depending on the DRE and PSA results, to confirm the diagnosis, a specialised doctor—usually a urologist—will need to perform additional tests such as a biopsy of the prostate, magnetic resonance imaging (MRI) or computerised tomography (CT) scans.

If cancer is diagnosed, additional tests will be undertaken to determine the best course of treatment.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The main goal for treating mCRPC is to control symptoms and slow progress.

First-line treatment options for mCRPC patients for whom chemotherapy is not indicated includes enzalutamide (NICE TA377), abiraterone (NICE TA387), and, since February 2024, olaparib with abiraterone (NICE TA951).[11–14]

As such, the proposed position of talazoparib with enzalutamide is alongside olaparib with abiraterone, enzalutamide and abiraterone as first-line treatment options for mCRPC.

A summary of the clinical pathway of care and position of talazoparib with enzalutamide is presented in the Figure 1 below.

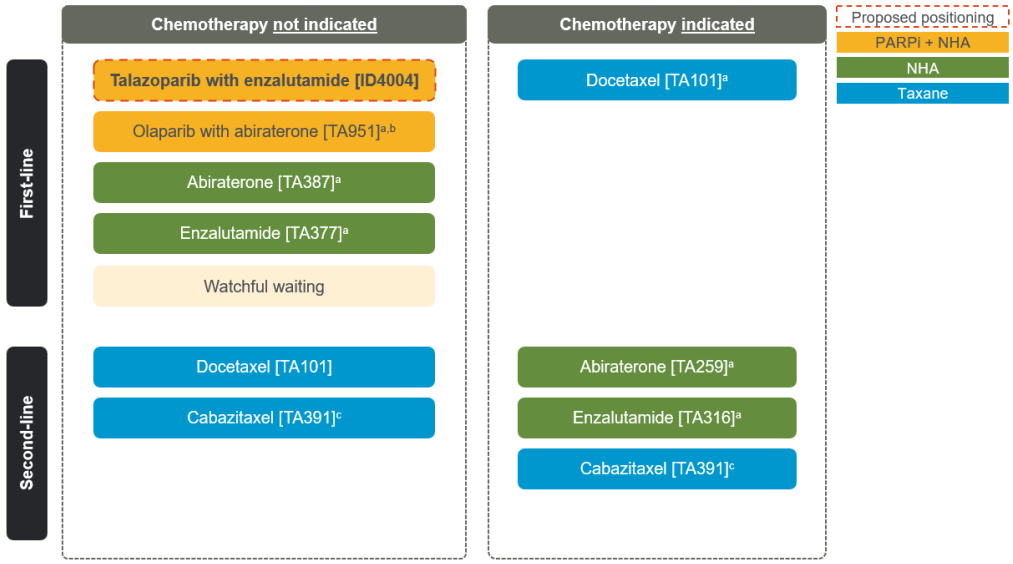


Figure 1. Clinical Pathway and proposed positioning of Talazoparib in 1L mCRPC

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Talazoparib plus Enzalutamide is a medicine for patients with advanced prostate cancer. The TALAPRO-2 trial tested this medicine on 805 patients who had this type of cancer. The trial looked at how long the patients lived, how safe the medicine was, how patients felt and how they reported their own health whilst on the medicine.[15]

The trial compared two groups of patients: one group got Talazoparib plus Enzalutamide, and the other group got a placebo (dummy pill) plus Enzalutamide. The results showed that:

1) The patients who got Talazoparib plus Enzalutamide felt slightly worse in their overall health and quality of life, but not deemed to be enough to make a big difference, and

2) The patients who got Talazoparib plus Enzalutamide did not have much change in their physical, emotional, social, and role functioning. The time to worsening in overall health and quality of life was longer in patients receiving this medicine, which suggests it controlled their disease for longer.

These results help us understand the benefits and risks of Talazoparib plus Enzalutamide, when compared to treatment with enzaluatamide alone.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Talazoparib works by causing certain cancer cells to die or by slowing their growth. There are some DNA repair machinery in all cells, one of which is called PARP. The repair of damaged DNA by PARP can enable cancer cells to survive and replicate, which causes tumours to grow. [16,17]

Talazoparib stops PARP from working, this is summarised in Figure 2 below.

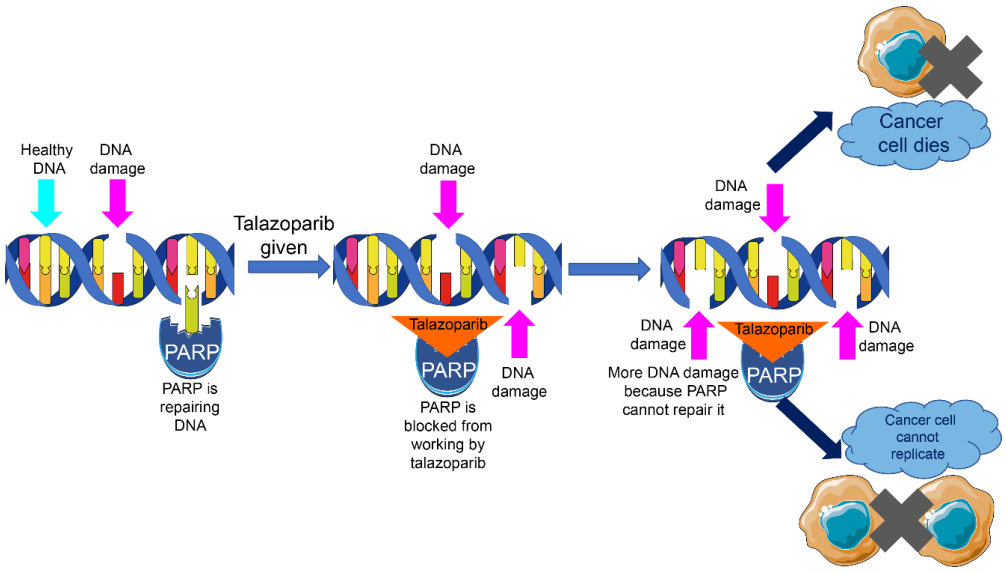


Figure 2. How talazoparib works to slow cancer cell growth and cause cancer cell death

When talazoparib blocks the activity of PARP, this means that:

- DNA damage in cancer cells cannot be repaired
- the cancer cell cannot replicate because they have too much DNA damage
- the cancer cells develop so much DNA damage that they die.

Like many medicines used in the treatment of cancers, it may cause some side effects.

Full details of Talazoparib, including how it works, how to take the medicine, list of known side effects and people who should not take Talazoparib, are available in the Summary of Product

Characteristics at: Talzenna 0.25 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Patient Leaflet: Talzenna 0.25 mg hard capsules - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

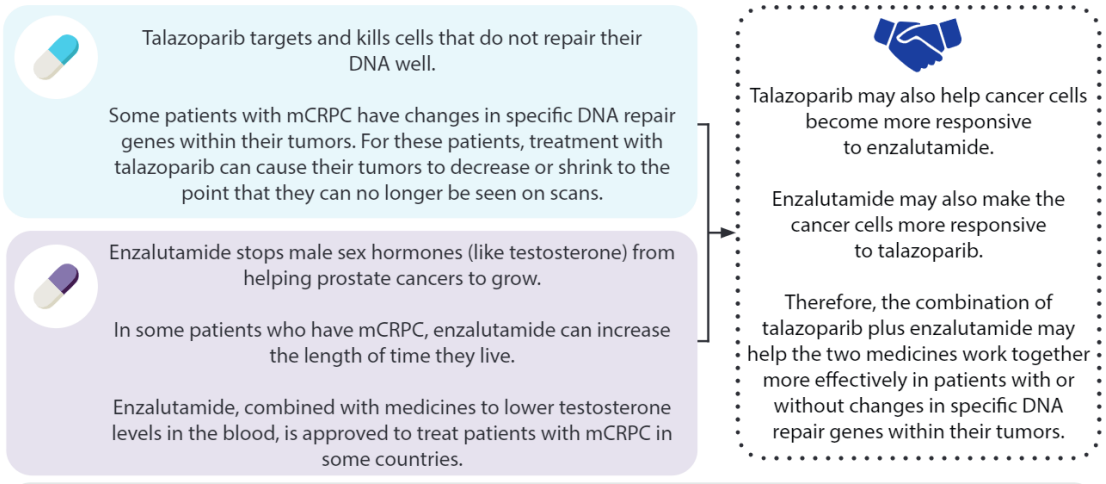
If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Yes, this medicine is intended to be used in combination with enzalutamide.

Enzalutamide is a Novel Hormonal Agent (NHA) that targets the androgen receptor signalling pathway, which is responsible for binding certain hormones which facilitates cell growth leading to tumour formation. By targeting the androgen receptor pathway, Enzalutamide prevents binding into the receptor and consequently leads to less cell growth.

There is a combined effect when PARP inhibition and NHAs are used in combination, increasing their effectiveness compared to either agent alone, where androgen blockade and sensitivity to PARP inhibition may be synergistic (have a great combined effect). This synergistic effect leads to delay in disease progression, potentially delay in the use of subsequent therapies and may improve the survival of the patients.



Full details of Enzalutamide, including how it works, how to take the medicine, list of known side effects and people who should not take Enzalutamide, are available in the Summary of Product Characteristics at: Xtandi 40 mg film coated tablets (Great Britain) - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Patient Leaflet (PIL): Xtandi 40 mg film coated tablets (Great Britain) - Patient Information Leaflet (PIL) - (emc) (medicines.org.uk)

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose is 0.5 mg talazoparib in combination with 160 mg enzalutamide once daily. They are both taken orally as tablets, this treatment regimen can be taken at home. [18]

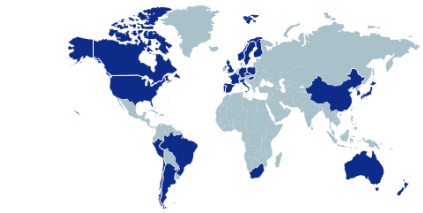
Patients should be treated until disease progression or unacceptable toxicity occurs.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

TALAPRO-2 is the on-going clinical trial for this treatment option, which is undergoing in 26 countries currently as shown in the Figure 3 below. This study is registered with ClinicalTrials.gov (NCT03395197) and is ongoing.[19]



Argentina
Australia
Belgium
Brazil
Canada
Chile
China
Czech Republic
Finland
France
Germany
Hungary
Israel
Italy
Japan
New Zealand
Norway
Peru
Poland
Portugal
Republic of Korea
South Africa
Spain
Sweden
UK
USA

Figure 3. 26 countries where TALAPRO-2 is on-going

The main aim of TALAPRO- 2 is to find out if combining talazoparib plus enzalutamide as a patient's first treatment for mCRPC will increase the length of time they live without their cancer getting worse or the patient dying compared with a placebo plus enzalutamide. Researchers also looked at other outcomes such as how treatment affected the size and number of tumours and any side effects the patients may have.[20]

Before starting the study, all patients underwent DNA testing to look for changes in specific DNA repair genes within their tumours. Both patients with and without these changes took part in the study.

The patients in the talazoparib plus enzalutamide group and the placebo plus enzalutamide group had similar characteristics when they started the study. About half of all patients in the study were 71 years or older when they started the study.

Between Jan 7, 2019, and Sept 17, 2020, there were 805 patients with mCRPC enrolled for this trial, all patients had mild (or no) symptoms. A summary of the inclusion criteria is shown in the Figure 4 below.

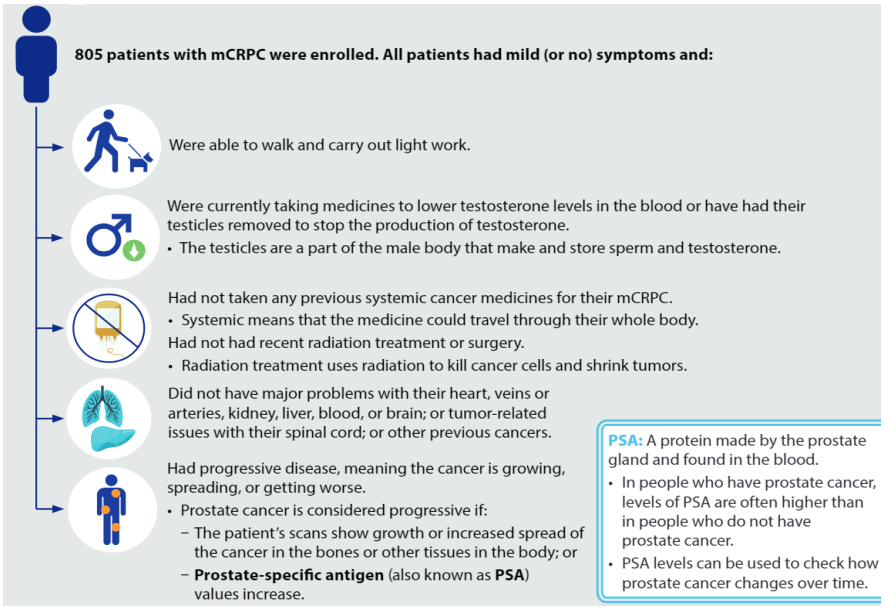
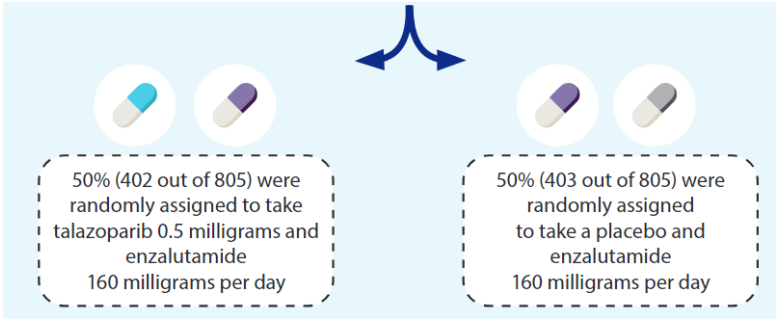


Figure 4. Characteristics of patients enrolled in TALAPRO-2

All 805 patients of the study took either talazoparib with enzalutamide (n=402) or enzalutamide with placebo (n=403).



More detail on the trial can be found in the publication: [Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial (thelancet.com)]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

These results are based on the interim analysis of the trial outcomes on the data cutoff on 16th August 2022 (the primary analysis of Talapro-2). These results supported the licensing of talazoparib plus enzalutamide.

Median follow-up for radiographic Progression Free survival (rPFS) was 24·9 months for the talazoparib group and 24·6 months for the placebo group. At the planned primary analysis, median rPFS was not reached for talazoparib plus enzalutamide and 21·9 months for placebo plus enzalutamide. Treatment with talazoparib plus enzalutamide resulted in a 37% lower risk of radiographic progression (blinded independent central review) or death than placebo plus enzalutamide.[19]

Overall survival data are immature; 123 (31%) of 402 patients in the talazoparib group and 129 (32%) of 403 in the placebo group had died at data cutoff.[19]

Confirmed objective response rate in patients with measurable disease at baseline was 62% (74 of 120) for the talazoparib group and 44% (58 of 132) for the placebo group, with a complete response in 45 (38%) of 120 and 24 (18%) of 132 patients, respectively. Treatment with talazoparib plus enzalutamide significantly prolonged the time to PSA progression, time to initiation of cytotoxic chemotherapy.[19]

Summary of results [20]:

- When comparing the talazoparib plus enzalutamide group with the placebo plus enzalutamide group, patients who took talazoparib plus enzalutamide had a reduced risk of their cancer getting worse or dying. Over the course of the study, the talazoparib plus enzalutamide group had a 37% (37 in 100) reduced risk of their cancer getting worse or dying.

- Both patients with and without changes in specific DNA repair genes had a reduced risk of their cancer getting worse or the patient dying if they took talazoparib plus enzalutamide compared with a placebo plus enzalutamide.

- Early results suggest that patients who took talazoparib plus enzalutamide had a higher chance of living longer than those who took a placebo plus enzalutamide. The full meaning of these results will be clearer as the study continues.

- Patients who took talazoparib plus enzalutamide were more likely to have a longer time before the PSA levels in their blood started to rise than those who took a placebo plus enzalutamide.

- About half of the patients who took talazoparib plus enzalutamide had 36 months or longer (vs. 35 months in the enzalutamide plus placebo group) before their cancer got worse again or they died while receiving their new cancer treatment.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

PROs were assessed[15], using the EORTC QLQ-C303, EORTC QLQ-PR25, the Brief Pain Inventory-Short Form (BPI-SF) and European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L), at:

- Baseline
- Scheduled visits (every 4 weeks up to week 53, then every 8 weeks) until progression
- Safety (at treatment discontinuation)
- Long-term follow-up visits (every 12 weeks)

Mean change from baseline in individual GHS/QoL, symptom, and functional scales were calculated.

Results[15]
Compared with placebo and enzalutamide (PBO + ENZA), in the Talazoparib plus Enzalutamide (TALA + ENZA) arm there was

1) a modest deterioration disfavouring GHS/QoL (deterioration was not clinically meaningful based on the predefined threshold), and

2) a maintenance in all functioning scales. TTD in GHS/QoL was significantly longer with TALA + ENZA vs PBO + ENZA, reflecting improved disease control. These results complement the benefit-risk assessment of TALAPRO-2.

Abbreviation: EORTC QLQ-PR25=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; PRO=patient-reported outcomes; QoL=quality of life; GHS=global health status; TTD=time to definitive deterioration

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

During all clinical trials, the safety of the trial treatments is monitored by recording any unexpected medical problems the people have. These are known as adverse events (AEs), which may or may not be related to the study treatment the participant is receiving. AEs can vary in their severity, so they are recorded as mild, moderate, or severe. Severity is how much an AE affects someone's health. Some AEs can be life threatening; these are also known as serious AEs.

The AEs that are shown in a clinical trial may be side effects caused by the treatment, but this can be uncertain. A lot of research is needed to know if an AE is a side effect of a drug. However, researchers can learn about the possible side effects of a drug by learning about the AEs during a

clinical trial. After a drug is approved it can be better understood by studying data from thousands of people taking the treatment in routine clinical care, which is known as a real-world evidence study. This also helps researchers and doctors better understand side effects.

Almost all patients in both groups had adverse events. The most common adverse events included:[19,20]

- A reduction in the number of red blood cells in the patient's blood, also called anaemia
- Excessive tiredness or exhaustion
- A reduction in the number of neutrophils in the patient's blood. (A neutrophil is a type of white blood cell that helps fight infections)
- A reduction in the number of platelets in the patient's blood (Platelets help the blood clot)

Side effects were generally managed by adjusting how much of the medicines a patient took. This means they could switch to a lower amount of medicine or stop taking the medicine for a short time. Of the 398 patients in the study, 33 (8%) stopped taking talazoparib because of anaemia. No patients in the talazoparib plus enzalutamide group died due to the side effects of the medicine they took. Two patients in the placebo plus enzalutamide group died due to the side effects related to the medicine they took. [19,20]

Overall, the results from TALAPRO-2 suggest that the potential side effects of talazoparib are manageable.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

- This treatment regimen can be taken at home.
- Over the course of the study, the talazoparib plus enzalutamide group had a 37% (37 in 100) reduced risk of their cancer getting worse or dying.
- Early results suggest that patients who took talazoparib plus enzalutamide had a higher chance of living longer than those who took a placebo plus enzalutamide. The full meaning of these results will be clearer as the study continues.

- About half of the patients who took talazoparib plus enzalutamide had 36 months or longer (vs. 35 months in the enzalutamide plus placebo group) before their cancer got worse again or they died while receiving their new cancer treatment.

- The reduced effect of treatment upon people's lives and wellbeing may enable them to spend more time on activities that are important to them and feel in better health, than if they were having chemotherapies.

- The current standard of care for patients who are eligible for a PARP inhibitor + NHA combination is olaparib with abiraterone. There are patients who may not be eligible for this treatment regimen because of cardiac issues, uncontrolled diabetes etc. This treatment will provide an additional option for all eligible patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

Like all anticancer therapies, talazoparib plus enzalutamide is associated with some side effects. The most common side effects are anaemia, neutropenia, and thrombocytopenia but a minority of patients may experience other side effects.

See the Summary of Product Characteristics at:
Talzenna 0.25 mg hard capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Xtandi 40 mg film coated tablets (Great Britain) - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by

patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

Model Structure:

- A simple cost comparison model has been included as part of the NICE evidence submission.
    - A cost comparison model compares the cost of the new treatment incurred by the National Health Service (NHS) to the cost of the comparator to the NHS. In this case Talazoparib plus Enzalutamide was compared to:
        - Olaparib plus Abiraterone
    - The model also includes cost for:
        - Drug and Disease monitoring cost: The costs associated with monitoring patients on treatment, such as blood tests, GP visits, X-rays and scans etc.
        - Drug treatment costs: the total costs of treatment associated with both combinations.
        - Adverse events and Skeletal related events (SREs) management cost: The adverse events considered more severe (grade 3 and 4) reported in the respective key clinical trials for both combinations were included in the economic model. Only AEs which affected at least 5% of patients were included. Similarly, the key skeletal related events associated with both treatments were included to the model to assess the management costs associated with it.
- The model considers the chosen time horizon as 30 years, as this was considered long enough to cover a patient.

Modelling how much Talazoparib plus enzalutamide extends life

PFS (the amount of time before a patient experiences a worsening in their disease) was used to estimate the amount of time patients are on treatment, since both treatments are advised to be given until disease progression occurs. Based on the finding from the Network Meta-Analysis (NMA), it was found that the rPFS was similar for both treatments, so, similar duration of treatment was assumed for both. The model needs to measure the costs over a patient lifetime, however clinical trials are only typically conducted for a few years. Therefore, the rPFS from TALAPRO-2 had to be extrapolated to estimate the total treatment duration over the full time horizon.

Uncertainty

The model is associated with some uncertainty. Firstly, to estimate the long-term total costs, extrapolation methods were used. As such there is uncertainty in how accurately the extrapolations reflect reality. Secondly, it was assumed that the clinical effectiveness of both drugs is similar based on the results of the Network Meta-Analysis (NMA), However, as they were not directly compared in a clinical trial, there is some uncertainty relating to this estimation method. Whilst there were some limitations to the method used, it was considered the best available approach for estimating the comparative effectiveness between these treatment options based on the available evidence.

Additional Information: As the economic model focuses on the associated costs of managing patients on talazoparib plus enzalutamide compared to olaparib plus abiraterone, it does not capture any wider benefits talazoparib plus enzalutamide provides, for example impact on quality of life.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

For patients eligible for a PARP inhibitor/NHA combination, the only option at present is a combination containing abiraterone. Clinicians have a number of NHA options in mCRPC, including both enzalutamide and abiraterone, and the choice of the most appropriate NHA for a particular patient is multifactorial. Where the NHA of choice in mCRPC is not abiraterone, there is currently no option available for these patients to receive PARP inhibitor/NHA combination therapy, creating a potential inequality in access. In addition, olaparib with abiraterone is contraindicated for some patients due to the associated risks of cardiotoxicity and challenges associated with steroid-exposure, such as uncontrolled diabetes, infection, osteoporosis, osteopenia, and gastro-intestinal bleeding. For those reasons, UK clinical experts noted that there is a need for new treatments to ensure they have a range of effective options to treat patients.

3l) Equalities

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

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

No equality issues related to the use of talazoparib with enzalutamide for the treatment of mCRPC have been identified.

Around 1 in 6 men develop prostate cancer and this disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer.[21] A broader range of treatment options will help to provide broader access and equity in outcomes for patients of all ethnicities

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Here are some further resources, where you can find out more background information, which may be relevant to prostate cancer or talazoparib. Cancer Research UK information about: ○ Prostate cancer: Prostate cancer | Cancer Research UK Published clinical trial data: ○ TALAPRO-2 (Talazoparib plus Enzalutamide): Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial (thelancet.com) ○ PROpel (Olaparib plus Abiraterone): Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer (nejm.org) Further information on NICE and the role of patients**:** ○ Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE ○ NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE ○ EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ ○ EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf ○ National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ ○ INAHTA: http://www.inahta.org/ ○ European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

DRE: digital rectal examination, where doctor or nurse insert a gloved, lubricated finger into the rectum to physically feel for the presence of any tumours. If a potential problem is detected, they will order blood testing.

mCRPC: metastatic castration-resistant prostate cancer. Prostate cancer that has spread beyond the prostate gland is no longer responsive to or continues to progress despite androgen deprivation therapy with drugs or castration. Sometimes also called hormone-relapsed metastatic prostate cancer.

NMA (Network meta-analysis): A statistical method used to compare multiple treatments at once by analysing data from various trials together.

Patient information leaflet: A document that offers guidelines for patinets on how to use a medicine safely and properly.

PSA (Prostate specific antigen): A protein made by normal and cancerous cells in the prostate. Elevated PSA levels in the blood can suggest prostate cancer but can also be caused by other conditions like benign prostatic hyperplasia (BPH) or prostatitis (inflammation of the prostate gland).

PSA test: A blood test used to measure the amount of prostate specific antigen (PSA) in the blood.

rPFS: The duration from the start of the trial to the first noticeable evidence of disease worsening seen through imaging, or until death, whichever comes first.

Summary of Product Characteristics: A document describing the properties and the officially approved conditions for a medicine, providing essential information for healthcare professionals on its safe and effective use.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. UK EMC. Talzenna 0.25 mg hard capsules - Summary of Product Characteristics (SmPC). Accessed August 11, 2024. https://www.medicines.org.uk/emc/product/10734/smpc#gref

2. Prostate cancer statistics | Cancer Research UK. Accessed August 3, 2024. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer

3. Sung H, Ferlay J, Siegel RL, 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):209-249. doi:10.3322/caac.21660

4. Shore N, Oliver L, Shui I, et al. Systematic Literature Review of the Epidemiology of Advanced Prostate Cancer and Associated Homologous Recombination Repair Gene Alterations. *J Urol*. 2021;205(4):977-986. doi:10.1097/JU.0000000000001570

5. Francini E, Gray KP, Shaw GK, et al. Impact of new systemic therapies on overall survival of patients with metastatic castration-resistant prostate cancer in a hospital-based registry. *Prostate Cancer Prostatic Dis*. 2019;22(3):420-427. doi:10.1038/s41391-018-0121-2

6. Chowdhury S, Bjartell A, Lumen N, et al. Real-World Outcomes in First-Line Treatment of Metastatic Castration-Resistant Prostate Cancer: The Prostate Cancer Registry. *Target Oncol*. 2020;15(3):301-315. doi:10.1007/s11523-020-00720-2

7. Holmstrom S, Naidoo S, Turnbull J, Hawryluk E, Paty J, Morlock R. Symptoms and Impacts in Metastatic Castration-Resistant Prostate Cancer: Qualitative Findings from Patient and Physician Interviews. *The Patient*. 2019;12(1):57-67. doi:10.1007/s40271-018-0349-x

8. Real-world health-related quality of life and caregiver need in patients with metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. | Journal of Clinical Oncology. Accessed August 3, 2024. https://ascopubs.org/doi/10.1200/JCO.2022.40.6_suppl.054

9. Saad F, Fleshner NE, So A, et al. The burden of symptomatic skeletal events in castrate-resistant prostate cancer patients with bone metastases at three Canadian uro-oncology centres. *Can Urol Assoc J J Assoc Urol Can*. 2019;12(12):370-376. doi:10.5489/cuaj.5053

10. Sathiakumar N, Delzell E, Morrisey MA, et al. Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999-2006. *Prostate Cancer Prostatic Dis*. 2011;14(2):177-183. doi:10.1038/pcan.2011.7

11. Overview | Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen | Guidance | NICE. June 27, 2012. Accessed August 3, 2024. https://www.nice.org.uk/guidance/ta259

12. Overview | Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel | Guidance | NICE. May 25, 2016. Accessed August 3, 2024. https://www.nice.org.uk/guidance/ta391

13. Overview | Enzalutamide for treating hormone-sensitive metastatic prostate cancer | Guidance | NICE. July 7, 2021. Accessed August 3, 2024. https://www.nice.org.uk/guidance/ta712

14. NICE. Single Technology Appraisal: Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920] Committee Papers. 2023. February 7, 2024. Accessed August 3, 2024. https://www.nice.org.uk/guidance/ta951

15. Agarwal N, Azad A, Matsubara N, et al. Patient-reported outcomes (PROs) among men receiving talazoparib (TALA) + enzalutamide (ENZA) vs placebo (PBO) + ENZA as first-line (1L) treatment for metastatic castration-resistant prostate cancer (mCRPC): Results from a phase 3 study (TALAPRO-2). *J Clin Oncol*. 2023;41(16_suppl):5013-5013. doi:10.1200/JCO.2023.41.16_suppl.5013

16. Sonnenblick A, de Azambuja E, Azim HA, Piccart M. An update on PARP inhibitors--moving to the adjuvant setting. *Nat Rev Clin Oncol*. 2015;12(1):27-41. doi:10.1038/nrclinonc.2014.163

17. Lord CJ, Ashworth A. The DNA damage response and cancer therapy. *Nature*. 2012;481(7381):287-294. doi:10.1038/nature10760

18. Search Results - (emc). Accessed August 3, 2024. https://www.medicines.org.uk/emc/search?q=talzenna

19. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Lond Engl*. 2023;402(10398):291-303. doi:10.1016/S0140-6736(23)01055-3

20. Agarwal N, Azad AA, Carles J, et al. Plain language summary of the results from the TALAPRO-2 study: Talazoparib plus enzalutamide versus placebo plus enzalutamide for patients with advanced prostate cancer. *Future Oncol*. 2024;0(0):1-13. doi:10.1080/14796694.2024.2362108

21. Delon C, Brown KF, Payne NWS, Kotrotsios Y, Vernon S, Shelton J. Differences in cancer incidence by broad ethnic group in England, 2013-2017. *Br J Cancer*. 2022;126(12):1765-1773. doi:10.1038/s41416-022-01718-5

theNATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID4004_Prostate talazoparib clarification questions_24APR25_[noCON]	1	No	24/04/2025
ID4004_Prostate talazoparib clarification questions_28JUL25_[noCON]	2	No	28/07/2025

Section A: Clarification on effectiveness data

A1. Please can the company clarify whether the literature searches have been updated for this systematic review (since 8 August 2024)?

Pfizer and NICE agreed that literature searches would not be updated for the purposes of this addendum to maintain the shared objective of keeping the process pragmatic and minimising further delays to patient access. From carrying out a desktop search we can confirm all relevant landmark phase III clinical trials have been considered and data from the most recent readouts of these trials has been used to inform our cost-effectiveness analysis.

A2. Priority: Subsequent treatments in the key trials:

a) **Please present a table of subsequent treatments received by people in each arm of TALAPRO-2 at the latest data cut.**
b) **Please present a table of subsequent treatments received in each arm in the PROpel trial.**
c) **Please present a table of subsequent treatments received in each arm in the COU-AA302 trial.**
d) **Please present a table of subsequent treatments received in each arm in the PREVAIL trial.**

TALAPRO-2 trial is a multinational study, which may lead to discrepancies in subsequent therapies patients receive after disease progression compared to clinical practices in the UK. Notably, re-treatment with novel hormone therapy (NHT) is prohibited in the UK and is not endorsed by the European Society for Medical Oncology (ESMO) guidelines.[1,2] Furthermore, within NICE TA951, experts consulted by the company emphasised that NHT retreatment is neither allowed nor considered to significantly impact patients' survival outcomes.[1]

According to UK clinical experts consulted by Pfizer, the most likely treatment options following progression from talazoparib and enzalutamide would be cytotoxic chemotherapy, such as docetaxel or cabazitaxel, or treatment with radium-223.

In PROpel and TALAPRO-2, most patients underwent cytotoxic chemotherapy following disease progression, reflecting common clinical practice in the UK.[3,4] The PROpel analysis specifically concentrated on patients who underwent additional

treatment, meaning the percentages for each type of subsequent treatment were calculated based on the number of patients who received further treatment after disease progression (Table 2). In contrast, the TALAPRO-2 study included all patients in Cohort 1 (all-comers, Table 1), with the percentages for each type of treatment determined based on the intention-to-treat population.

a) Subsequent treatments received by people in each arm of cohort 1 in TALAPRO-2 at the latest data cut are presented in Table 1.[5]

Table 1. Subsequent treatments in each arm of TALAPRO-2 – All-comers (cohort 1) population at final data cutoff 3rd September 2024

	Talazoparib + Enzalutamide (N=398)	Placebo + Enzalutamide (N=401)	Total (N=799)
Post-baseline antineoplastic therapy use	**n (%)**	**n (%)**	**n (%)**
Patients taking any of the selected post-baseline therapy	145 (36.4)	201 (50.1)	346 (43.3)
Taxane-Based Therapy	102 (25.6)	149 (37.2)	251 (31.4)
Cabazitaxel	46 (11.6)	66 (16.5)	112 (14.0)
Docetaxel	90 (22.6)	133 (33.2)	223 (27.9)
Paclitaxel	1 (0.3)	2 (0.5)	3 (0.4)
Second Generation Androgen Receptor Inhibitors	22 (5.5)	25 (6.2)	47 (5.9)
Apalutamide	1 (0.3)	3 (0.7)	4 (0.5)
Darolutamide	1 (0.3)	1 (0.2)	2 (0.3)
Enzalutamide	20 (5.0)	22 (5.5)	42 (5.3)
Rezvilutamide	1 (0.3)	0	1 (0.1)
Radiopharmaceuticals	36 (9.0)	44 (11.0)	80 (10.0)
Lutetium-177	15 (3.8)	16 (4.0)	31 (3.9)
PSMA-Targeted Radiopharmaceuticals	0	1 (0.2)	1 (0.1)
Radium	20 (5.0)	27 (6.7)	47 (5.9)
Strontium	0	1 (0.2)	1 (0.1)
Therapeutic Radiopharmaceuticals	1 (0.3)	1 (0.2)	2 (0.3)
Single-agent PARP Inhibitor Therapies	6 (1.5)	15 (3.7)	21 (2.6)
Olaparib	6 (1.5)	15 (3.7)	21 (2.6)
Cellular Immunotherapy	1 (0.3)	1 (0.2)	2 (0.3)

Sipuleucel-T	1 (0.3)	1 (0.2)	2 (0.3)
Androgen Biosynthesis Inhibitors	44 (11.1)	68 (17.0)	112 (14.0)
Abiraterone	44 (11.1)	68 (17.0)	112 (14.0)
Other Cytotoxic Chemotherapy	5 (1.3)	19 (4.7)	24 (3.0)
Carboplatin	4 (1.0)	15 (3.7)	19 (2.4)
Cisplatin	1 (0.3)	6 (1.5)	7 (0.9)

Patients could be counted in more than one subsequent therapy.
Source: TALAPRO-2 1.0 Interim All-comers CSR – Table 14.1.4.10.[5]

b) Subsequent treatments received by people in each arm in the PROpel trial are presented in Table 2.[4]

Table 2. Subsequent treatments received in each arm in the PROpel trial

	Abiraterone and Olaparib (N=132)	**Abiraterone and Placebo (N=173)**
Cytotoxic Chemotherapy	91 (68.9)	130 (75.1)
Hormonal Therapy	46 (34.8)	56 (32.4)
Immunotherapy	11 (8.3)	14 (8.1)
Targeted Therapy	6 (4.5)	14 (8.1)
Systemic Therapy	1 (0.8)	5 (2.9)
PARP Inhibitor	0	3 (1.7)
Other	3 (2.3)	7 (4.0)

Data are n(%). Patients could be counted in more than one anticancer therapy.
Source: Clarke et al. 2022 – Table S3[4]

c) Subsequent treatments received by people in each arm in the COU-AA302 trial are presented in Table 3.[6]

Table 3. Subsequent treatments received in each arm in the COU-AA302 trial

	Abiraterone acetate plus prednisone	**Placebo plus prednisone**
Patients	546	542
Taxane Chemotherapy		
Docetaxel	261 (48.0)	272 (50.2)
Cabazitaxel	4 (<1)	3 (<1)
Androgen Synthesis Inhibitor		
Abiraterone Acetate	13 (2.4)	80 (14.8)
Ketoconazole	36 (6.6)	56 (10.3)
Androgen Receptor Antagonist (Enzalutamide)	20 (3.7)	4 (<1)
Immunotherapy (Sipuleucel-T)	31 (5.7)	20 (3.7)

Data are n(%).
Source: de Bono et al. 2017 – Table 3.[6]

d) Subsequent treatments received by people in each arm in the PREVAIL trial are presented in Table 4.[7]

Table 4. Subsequent treatments in each arm in the PREVAIL trial

	Enzalutamide (N=872)	Placebo (N=845)
Patients taking ≥ 1 subsequent therapy, n(%)	457 (52.4)	685 (81.1)
Docetaxel	358 (41.1)	504 (59.6)
Abiraterone Acetate[a]	256 (29.4)	417 (49.3)
Enzalutamide[b]	21 (2.4)	249 (29.5)
Cabazitaxel	79 (9.1)	149 (17.6)
Radium-223 dichloride	16 (1.8)	22 (2.6)
Sipuleucel-T	17 (1.9)	11 (1.3)

[a] Concomitant abiraterone acetate use was allowed before study drug discontinuation in patients with confirmed radiographic progression or a skeletal-related event.
[b] Placebo patients who received enzalutamide in the open-label extension period are included in the subsequent therapy of enzalutamide under the placebo column.
Source: Beer et al. 2016 – Table 1.[7]

A3. It was not clear from the MAIC write-up in Section 1.21 of the Addendum, what you consider to be prognostic factors and what you consider to be treatment effect modifiers. Please detail the relevant prognostic factors for this appraisal, and separate to that, detail the relevant treatment effect modifiers for this appraisal.

Since an unanchored MAIC was conducted, it was essential to adjust for all prognostic factors and treatment effect modifiers. In the primary analysis, we adjusted for all identified factors (as per Section 1.121 in the company addendum) and did not distinguish between prognostic factors and treatment effect modifiers. Consequently, the results of the primary analysis accounted for both prognostic factors and treatment effect modifiers, which were identified and ranked in order of importance based on previously published analyses by Armstrong et al. 2018[8] and refined based on external clinician opinion prior to analysis, adhering to the guidance from NICE Technical Support Document (TSD) 18[9] (see Table 3 in the company addendum).

A4. Priority: Ensuring proportionality is crucial for the validity of MAIC analyses, as it helps to avoid bias and ensure that the results are not unduly influenced by the specific choice of weights. Please present visual and statistical tests of proportionality for the MAIC.

The comparative efficacy of talazoparib with enzalutamide versus olaparib with abiraterone for rPFS and OS was estimated using Cox proportional hazards (PH) model. The PH assumption was assessed for the MAIC (i.e. adjusting for all available

ranked prognostic factors and effect modifiers) for talazoparib with enzalutamide versus olaparib with abiraterone, for both rPFS and OS. Visual inspection of the log-cumulative hazard plots (Figure 1 & 2) and Schoenfeld residual plots (Figure 3 & 4) ********** Grambsch-Therneau test for proportional hazards assumption was conducted and ********** Results from these statistical tests of proportionality highlight the validity of the MAIC as an appropriate ITC methodology for comparing rPFS and OS outcomes between talazoparib with enzalutamide and olaparib with abiraterone.

**********, it is not relevant to the methodology used in the company base case. In the company base case, the MAIC is used to produce reweighted IPD, and independent parametric curves are then fitted for each outcome and arm. Because independent parametric curves are fit for each arm and outcome, the outcomes are not reliant on a hazard ratio and therefore do not rely on an assumption of proportional hazards.

Figure 1. Log-cumulative hazard plot for rPFS – talazoparib with enzalutamide vs olaparib with abiraterone

Abbreviations: TALA+ENZA – talazoparib with enzalutamide; OLA+AAP – olaparib with abiraterone.

Figure 2. Log-cumulative hazard plot for OS – talazoparib with enzalutamide vs olaparib with abiraterone

Abbreviations: TALA+ENZA – talazoparib with enzalutamide; OLA+AAP – olaparib with abiraterone.

Figure 3. Schoenfeld residual for rPFS – talazoparib with enzalutamide vs olaparib with abiraterone

Figure 4. Schoenfeld residual for rPFS – talazoparib with enzalutamide vs olaparib with abiraterone

A5. Matching in the MAIC:

a) Please clarify why matching was not believed to be necessary for the MAIC, given the trial with summary data has a broader inclusion criterion on BPI-SF than TALAPRO-2.

b) What do you understand to be the risks associated with MAICs where no matching was conducted?

a) ***Eligibility criteria***

The eligibility criteria for TALAPRO-2 and PROpel were compared. Where appropriate, ***patients in the TALAPRO-2 population were matched to PROpel's eligibility criteria***. Specifically, patients from TALAPRO-2 were removed from the IPD set if they were not satisfied according to the eligibility criteria used in PROpel. The matching phase of the MAIC required that TALAPRO-2 had a broader patient population than PROpel.

The eligibility criteria for BPI-SF differed between TALAPRO-2 and PROpel. PROpel had no eligibility restrictions based on pain as per the Brief Pain Inventory Short Form (BPI-SF), making its inclusion criteria broader. In contrast, TALAPRO-2 required patients to have a score of ≤3 on question 3 of the BPI-SF (worst pain in the last 24 hours). Therefore, TALAPRO-2's patient cohort could only have a score between 0 and 3; whereas PROpel's patient cohort could have a score between 0 and 10. Given this difference, it was determined that all patients in TALAPRO-2 would meet the broader criteria of PROpel. Therefore, the removal of patients from the TALAPRO-2 IPD (i.e. matching) was not required to align the trials on BPI-SF criteria.

Stratification factors, prognostic factors, and treatment effect modifiers

Patients in TALAPRO-2 were then reweighted to adjust for imbalances in stratification factors, key prognostic factors, and treatment effect modifiers. Specifically, patients in TALAPRO-2 were stratified at randomisation by HRR mutation status and prior novel hormonal therapies (NHT) or taxane-based therapy in the castration-sensitive prostate cancer (CSPC) stage. To align with the PROpel population, patients in TALAPRO-2 were reweighted for each of

these stratification factors, as well as for prognostic factors and treatment effect modifiers identified from the published literature[8] and validated and ranked by a clinical expert. These factors are presented in Table 3 in the company addendum. This reweighting process involved upweighting patients who were underrepresented and downweighing those who were overrepresented to make the TALAPRO-2 cohort more similar to the PROpel cohort.

Reweighting was not possible for time to mCRPC from continuous ADT, neutrophil to lymphocyte ratio and BPI-SF. Time to mCRPC from continuous ADT and neutrophil-to-lymphocyte ratio were not adjusted for because these variables were not mutually reported in both PROpel and TALAPRO-2.

Similarly, BPI-SF was not adjusted for because the way this variable was reported in PROpel did not allow for adjustment. The distribution of scores for BPI-SF item 3 from PROpel is presented in Table 5.[4] Since 100% of the patients in TALAPRO-2 were required to have a BPI-SF score ≤3 on item 3, all patients in TALAPRO-2 would fall into the first two categories reported in PROpel. Therefore, we were unable to adjust the proportion for each category reported in PROpel (e.g., 0, <0-<4, 4-<6, 6-10).

After the reweighting process, the patient characteristics of TALAPRO-2 matched those of PROpel. The results of this exercise are presented in Table 4 in the company addendum. All mutually available factors reported in both trials were adjusted for in the MAIC analysis.

Table 5. Pain scores of patients at baseline in PROpel

BPI-SF Item 3 score	n (%)
0 (no pain)	133 (33.3)
>0 – <4 (mild pain)	151 (37.8)
4 – <6 (moderate pain)	53 (13.3)
6 – 10 (severe pain)	32 (8.0)
Missing	30 (7.5)

Source: Clarke et al. 2022 – Table S1.[4]

b) An inherent limitation with MAICs is that it is only possible to adjust for baseline variables that are mutually reported between trials, and unadjusted baseline variables can act as confounding, potentially limiting the true treatment effect. However, it is important to note that TALAPRO-2 and PROpel were similar across most eligibility criteria (e.g., age, ECOG PS, confirmation of prostate cancer, medical/surgical castration, documented metastatic disease, treatment naïve status in the mCRPC state, and evidence of progressive disease). These trials were deemed sufficiently similar, and their similarity was further validated by an external clinical expert. Furthermore, the observed imbalances in the identified treatment effect modifiers and prognostic factor variables were diminished once the patients in TALAPRO-2 were reweighted via adjusting as per the MAIC methodology, thereby further aligning the patient cohorts and reducing the potential for biased indirect treatment effects.

A6. Priority: Please conduct an indirect treatment comparison using an anchored approach, such as fractional polynomials, to address non-proportional hazards. This can be conducted either with or without adjustment for potential confounding treatment effect modifiers if you believe these to be an issue.

Pfizer has requested a timeline extension from NICE to deliver an indirect treatment comparison (ITC) using a fractional polynomial (FP) approach. Pfizer will provide results of ITC using a FP approach once completed.

Section B: Clarification on cost-effectiveness data

Updated company economic base case

The company have submitted an updated economic model with the following updates applied to the base case in response to the clarification questions in this section:

- Use of log-normal distribution to for rPFS and generalised gamma distribution for OS, for both treatment arms (question B4)
- Inclusion of the latest TTD data from TALAPRO-2 for talazoparib and enzalutamide, modelled separately (question B7a)
- Inclusion of the latest RDI data from TALAPRO-2 for talazoparib and enzalutamide, and data from published literature for olaparib with abiraterone (question B11)
- Inclusion of pharmacy dispensing costs for oral treatments (question B12b)
- Inclusion of background ADT costs (question B12b)
- Use of updated source of palliative care costs (Round et al. 2015[10]) and terminal care costs (TA951[1]) (question B16)

The company have also corrected the base case as per the following:

- Included weighted average calculations for anaemia (see question B13), CT scan, and radiation to bone costs to account for number of patients costed using each currency code
- Accounted for inflation in the cost for pathological bone fractures (sourced from TA951)
- Updated first- and second-line disease monitoring frequencies to accurately convert frequencies from weeks to months and make minor additional corrections

A summary of the updated base case results is presented in Table 6.

Table 6. Updated base case results

Question	Assumption	Incremental costs (£)	Incremental QALYs	ICER (£) (Individual change)
Original base case		[redacted]	[redacted]	[redacted]
B4	Log-normal rPFS and generalised gamma OS distributions (both arms)	[redacted]	[redacted]	[redacted]
B7a	TTD data for talazoparib and enzalutamide	[redacted]	[redacted]	[redacted]
B11	RDI data for talazoparib, enzalutamide, and olaparib with abiraterone	[redacted]	[redacted]	[redacted]
B12b	Pharmacy dispensing costs	[redacted]	[redacted]	[redacted]
B12b	Background ADT costs	[redacted]	[redacted]	[redacted]
B16	Palliative care and terminal care cost	[redacted]	[redacted]	[redacted]
Model corrections				
-	Weighted average for anaemia, CT scan, and radiation to bone costs	[redacted]	[redacted]	[redacted]
-	Inflation calculation for pathological bone fractures cost	[redacted]	[redacted]	[redacted]
-	First line disease monitoring frequencies and costs	[redacted]	[redacted]	[redacted]
-	Second line disease monitoring frequencies and costs	[redacted]	[redacted]	[redacted]
Updated base case		[redacted]	[redacted]	[redacted]

Abbreviations: ADT – Androgen deprivation therapy; CT – Computed tomography; ICER – Incremental cost-effectiveness ratio; OS – Overall survival; QALY – Quality-adjusted life years; RDI – Relative dose intensity; rPFS – Radiographic progression-free survival; TTD – Time to discontinuation

An overview of scenario analyses presented in response to clarification questions throughout this section is presented in Table 7. The results are discussed in further detail in response to the respective questions.

Table 7. Scenario analysis results

Question	Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER per QALY (£)
Updated base case		[redacted]	[redacted]	[redacted]
B4	Log-logistic rPFS and generalised gamma OS distributions (both arms)	[redacted]	[redacted]	[redacted]
B8	Excluding SREs	[redacted]	[redacted]	[redacted]
B12	Wastage for oral drugs	[redacted]	[redacted]	[redacted]
B14	+10% time spent on palliative care after discontinuation of subsequent treatments	[redacted]	[redacted]	[redacted]
B14	-10% time spent on palliative care after discontinuation of subsequent treatments	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; QALY – Quality-adjusted life years; SRE – Skeletal-related events.

Economics searches

B1. Economics searches:

a) Please can the company clarify whether the searches for health-related quality-of-life studies and healthcare resource use and economic evaluations have been updated since October 2022?

b) We note that the NICE guidelines manual states that searches must be rerun, if the initial search date is more than 12 months (preferably 6 months) from the intended publication date. In the report you stated that, in line with the pragmatic approach agreed with NICE, an update for the purposes of this appraisal has not been conducted. Did you have an agreement with NICE specifically related to the requirement to conduct update searches for this appraisal?

c) Given the time since the last searches were run, please present reasoning why we should not be concerned that relevant health-related quality-of-life studies containing utility data were published in the intervening period? This is the priority as literature data has been used to inform the model for post-progression utilities

d) Given the time since the last searches were run, please present reasoning why we should not be concerned that relevant healthcare resource use and economic evaluations were published in the intervening period?

a) Pfizer and NICE agreed that literature searches would not be updated for the purposes of this addendum to maintain the shared objective of keeping the process pragmatic and minimising further delays to patient access.

b) Please see response to B1 a).

c) Since submitting the company addendum, an update to the original systematic literature review (SLR) for health-related quality of life data in mCRPC has been rerun until 18th November 2024. Details of the search strategy and pre-defined PICOS criteria used screen studies are presented in Section 1 of the Appendix. In the updated SLR, two clinical studies and three economic evaluations were identified. Details of the utility values captured from the clinical studies and economic evaluations are presented in Table 8 and Table 9, respectively. Despite no new UK data being captured, it is of note that the utility values used in the economic evaluations for the progressed disease health state are all lower than the 0.685 value used in the economic base case in the company addendum (from TA377[11]); highlighting a conservative approach.

Table 8. Summary of utility values measured in clinical studies

Region	Trial; NCT Reference	Study Design/ Study Type	Patient Population	Treatment Arm	Timepoints Assessed	Utility Value	Baseline Utility Value [a]	Utility Value at Last Timepoint [a]	Utility Value change from baseline [a]
Clinical Trials									
Global	MAGNITUDE; NCT03748641. Rathkopf et al. 2024[12]	Phase 3 RCT	1L asymptomatic/ mildly symptomatic mCRPC	Niraparib + abiraterone acetate and prednisone	Baseline up to Cycle 31	EQ-5D-5L EQ-5D VAS	BRCA+ subgroup: EQ-5D-5L, Median (IQR): 0.8 (0.7-1) EQ-5D VAS, Median (IQR): 79 (68-90) Mean: 74.9 [b] HRR+ subgroup, Median (IQR): EQ-5D-5L 0.8 (0.7-1) EQ-5D VAS 79 (65-89)	BRCA+ subgroup: EQ-5D VAS, Mean: 76 [b]	NR

Region	Trial; NCT Reference	Study Design/ Study Type	Patient Population	Treatment Arm	Timepoints Assessed	Utility Value	Baseline Utility Value [a]	Utility Value at Last Timepoint [a]	Utility Value change from baseline [a]
				Placebo + abiraterone acetate and prednisone			BRCA+ subgroup: EQ-5D-5L, Median (IQR): 0.9 (0.7-1) EQ-5D VAS, Median (IQR): 80 (67-90) Mean: 75.3 [b] HRR+ subgroup, Median (IQR): EQ-5D-5L 0.8 (0.7-1) EQ-5D VAS 80 (70-90)	BRCA+ subgroup: EQ-5D VAS, Mean: 74.5 [b]	NR
Observational Studies									
Slovakia	Kuzma et al. 2024[13]	Prospective observational study	Chemotherapy-naïve mCRPC	Abiraterone acetate	Baseline, 3, 6, 9, and 12 months	EQ-5D-5L EQ-5D VAS	72.0 (13.2)	NR	LSMC (95% CI): [c] EQ-5D-5L -0.04 (-0.15; 0.06) EQ-5D VAS -1.93 (-12.24; 8.39)
				Enzalutamide			64.0 (13.1)		LSMC (95% CI): [c] EQ-5D-5L -0.16 (-0.26; -0.07) EQ-5D VAS -8.67 (-17.59; 0.25)

[a] Reported as mean (SD) unless otherwise specified.
[b] Value was digitized from a figure using DigitizeIt software.
[c] Mixed model for repeated measures adjusted least square mean change from baseline.
Abbreviations: 1L = first-line; CI = confidence interval; EQ-5D-5L = EuroQuol 5-Dimension 5-Level; HRR = homologous recombination repair; IQR = interquartile range; mCRPC = metastatic castration-resistant prostate cancer; NR = not reported; RCT = randomized control trial; SD = standard deviation; VAS = visual analogue scale.

Table 9. Summary of utility values reported in economic evaluations

Region	Reference	Study Type	Patient Population	Treatment Arm	Source of Utility Values	Reported utility values
US	Duru et al. 2024[14]	CUA	1L asymptomatic/ mildly symptomatic with BRCAm positive mCRPC	Niraparib + abiraterone acetate and prednisone	Published studies [a]	Progression-free disease: 0.76 Progressed disease: 0.37 Disutility grade ≥3: -0.58
China	Zeng et al. 2022[15]	CUA	Patients with bone mCRPC (unclear LOT)	Radium-223 + BSC	Tirado Mercier et al. 2018[16]	Progression-free without SSE: 0.617 Progression-free with SSE: 0.475 Progression without SSE: 0.511 Progression with SSE: 0.474
				BSC		Progression-free without SSE: 0.554 Progression-free with SSE: 0.475 Progression without SSE: 0.511 Progression with SSE: 0.474
Iran	Goudarzi et al. 2024[17]	CUA	Patients with mCRPC (unclear LOT, docetaxel-treated)	Enzalutamide	Okumura et al. 2021[18] Hagiwara et al. 2018[19]	Progression-free: 0.61 Progression: 0.31 Disutility anemia: 0.11 Disutility backpain: 0.06 Disutility bone pain: 0.06 Disutility diarrhoea: 0.2 Disutility fatigue: 0.47 Disutility neutropenia: 0.1 Disutility arthralgia: 0.041 Disutility vomiting: 0.09
				Abiraterone acetate		

[a] This reference was a conference poster, and the source of utility values were not specified

Abbreviations: 1L = first-line; BSC = best supportive care; CUA = cost-utility analysis; LOT = line of therapy; LSMC = least square mean change; mCRPC = metastatic castration-resistant prostate cancer; SSE = symptomatic skeletal event; US = United States

d) Please see response to B1 a).

Comparators

B2. Priority: As noted in the email already received from NICE, please include a comparison to enzalutamide within the economic model. As a pragmatic approach it is considered reasonable to do this based upon extrapolation of within trial data.

Pfizer has requested a timeline extension from NICE to develop and deliver a cost-utility analysis against enzalutamide monotherapy. Pfizer will provide results from the analysis once completed. rPFS and OS data that will inform the analysis will be derived from the final data cut of TALAPRO-2 (data cutoff 3rd September 2024).

Survival analysis

B3. Please provide updated versions of Tables 10 – 13 including the mean area under the curve for the full model time horizon in addition to the median and landmark estimates currently supplied

Tables 10–13 from the addendum have been updated to include mean area under the curve for each rPFS and OS parametric distribution (Table 10 to Table 13 below).

Table 10. Goodness-of-fit statistics and survival predictions for talazoparib with enzalutamide rPFS parametric distributions

Distribution	Goodness-of-fit				rPFS					
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)
KM data										
Log-normal										
Generalised gamma										
Log-logistic										
Exponential										
Gamma										
Gompertz										
Weibull										

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; rPFS – Radiographic progression-free survival

Table 11. Goodness-of-fit statistics and survival predictions for olaparib with abiraterone rPFS parametric distributions

Distribution	Goodness-of-fit				rPFS				
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	48 months (%)
TA951 base case (gen gamma)	-	-	-	-	-	23.0	NR	NR	28.2%
KM data									
Log-normal									
Generalised gamma									
Log-logistic									
Gamma									
Weibull									
Exponential									
Gompertz									

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; NR – Not reported; rPFS – Radiographic progression-free survival

Table 12. Goodness-of-fit statistics and survival predictions for talazoparib with enzalutamide OS parametric distributions

Distribution	Goodness-of-fit				OS							
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data												
Log-normal												
Log-logistic												
Generalised gamma												
Gamma												
Weibull												
Gompertz												
Exponential												

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; OS – Overall survival

Table 13. Goodness-of-fit statistics and survival predictions for olaparib with abiraterone OS parametric distributions

Distribution	Goodness-of-fit					OS						
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
TA951 base case (gen gamma)	-	-	-	-	-	43.0	87.7%	70.5%	NR	46.2%	Not reported	17.1%
KM data										-	-	-
Log-normal												
Generalised gamma												
Log-logistic												
Gamma												
Weibull												
Exponential												
Gompertz												

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; NR – Not reached; OS – Overall survival

B4. Priority: Please explain the kink in the generalised gamma curve in Figure 8. It looks like PFS is predicted to be higher than OS and is being limited. If this is the case, please justify selection of a curve which predicts a higher PFS than OS / reconsider curve selection.

The kink in the generalised gamma curve of Figure 8 of the addendum is the result of a limitation in the model which prevents rPFS from exceeding OS. To avoid this limitation, the company have revisited the base case parametric curve choice using the criteria described in NICE DSU TSD 14[20] to select the most appropriate curve based on statistical fit, visual fit, long-term plausibility, and clinical validation. Based on this, the updated base case uses the log-normal curve for rPFS and the generalised gamma curve for OS (for both treatment arms given that NICE DSU TSD 14[20] recommends the same distribution across both treatment arms). The justification for the selection of these curves is provided below.

As already mentioned in the company addendum, in TA951[1], six UK clinical experts with experience using abiraterone for treating first-line mCRPC were consulted to clinically validate the appropriate choice of extrapolation. The submitting company selected the generalised gamma distribution in the revised base case for OS following diagnostic, visual, statistical fit and hazard function assessments, and clinical expert validation. The committee also concluded that the generalised gamma was the most appropriate parametric curve for extrapolating OS. Therefore, in line with TA951, we do not feel it is appropriate to deviate from the curve selection for olaparib with abiraterone for OS but rather fix rPFS curve selection across both treatment arms so as to avoid rPFS from exceeding OS for talazoparib with enzalutamide (causing a kink in the rPFS curve).

Based on statistical fit, assessed using the sum rank of the AIC and BIC information criteria, the log-normal, log-logistic, and generalised-gamma curves are the most suitable curves for rPFS for both treatment arms. However, the generalised gamma curve is not an appropriate selection as rPFS eventually exceeds OS in the talazoparib with enzalutamide arm, which is implausible (causes a kink in the curve). As shown in Table 10 and 11 (question B3), the log-normal curve ranks best statistical fit for rPFS for talazoparib with enzalutamide and second best statistical fit for rPFS for olaparib with abiraterone. The log-logistic curve ranks best statistical fit for rPFS for olaparib

with abiraterone and third best statistical fit for rPFS for talazoparib with enzalutamide. Overall, while both log-normal and log-logistic are suitable choices for rPFS in the model base case, log-normal has marginally better statistical fit.

As displayed in Figure 8 and 9 of the company addendum, the log-normal and log-logistic curves have an acceptable visual fit for rPFS (for both treatment arms), and, as presented in Table 10 and 11, both align well with the trial KM data. In addition, the log-normal and log-logistic curve selection avoids the issue of rPFS exceeding OS (when OS is modelled by generalised gamma for both treatment arms).

In terms of external validity, as discussed in question B5a), the log-normal olaparib with abiraterone for rPFS aligns closely with TA951[1] estimates. Additionally, clinical expert opinion from three UK clinical experts sought in response to EAG clarification questions (April 2025) informed they would expect pessimistic median rPFS estimates, and therefore curves which reflect pessimistic median rPFS estimates would be the most appropriate for use. This guidance supports the use of the log-normal and log-logistic curves, given the associated median rPFS estimates (see Table 10 and 11).

In summary, based on the selection process described above, the new company base case uses the log-normal curve for rPFS and the generalised gamma curve for OS for both treatment arms. The incremental impact of using log-normal for rPFS and OS (for both treatment arms) on the original base case is presented in Table 14. A scenario adopting a log-logistic distribution for rPFS and generalised gamma for OS (for both treatment arms) on the updated base case is also presented in Table 15. Overall, both the log-normal and log-logistic curves are plausible options for modelling rPFS across both treatment arms in the economic model.

Table 14. Updated base case results, using log-normal distribution for rPFS and generalised gamma distribution for OS for both treatment arms

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Table 15. Scenario analysis results, using log-logistic distribution for rPFS and generalised gamma distribution for OS for both treatment arms

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

B5. Priority: One of the rationales provided for selection of the generalised gamma curve on page 38 is that it "was more conservative than the best statistical fitting curve" in TA951. This does not appear to be the case here (generalised gamma is the most optimistic curve in Figure 8).

a) Please compare the rPFS predictions in TA951 to those presented in here as you have done for OS on page 47.

b) In addition, if possible, please present a visual comparison of your fitted curves to the final agreed curves in TA951.

a) The rPFS predictions in TA951 are redacted, except for the month 48 landmark. However, as shown in Table 11, predicted rPFS at Month 48 when using the log-normal distribution (in line with the updated base case) is similar to the generalised gamma distribution used in TA951 ([redacted] vs 28.2%, respectively).

b) The rPFS parametric curves are redacted in TA951, so it is not possible to present a visual comparison of the fitted curves.

B6. Please provide updated versions of Figures 12 and 13 including numbers at risk for the Kaplan Meier data. Please investigate and correct the Excel issue causing the Kaplan Meier plot to appear to bend (particularly apparent for olaparib + abiraterone in Figure 12)

The curvature of the KMs observed in Figure 12 and Figure 13 of the addendum was a result of the 'smooth function' in Excel which is a visual effect only and does not impact the underlying KM data. Replacement figures have been provided below in Figure 5 and Figure 6 for rPFS and OS, respectively.

In line with the response to Question B4, the log-normal distribution parametric distributions have been presented in Figure 5 and Figure 6.

Figure 5. Talazoparib with enzalutamide and olaparib with abiraterone KMs for rPFS overlaid with the extrapolated parametric survival curves using log-normal distributions (with numbers at risk)

Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; KM – Kaplan-Meier; OLA – Olaparib; rPFS – Radiographic progression-free survival; TALA - Talazoparib

Figure 6. Talazoparib with enzalutamide and olaparib with abiraterone KMs for OS overlaid with the extrapolated parametric survival curves using log-normal distributions (with numbers at risk)

Abbreviations: ABI – Abiraterone; ENZA – Enzalutamide; KM – Kaplan-Meier; OLA – Olaparib; OS – Overall survival; TALA – Talazoparib

B7. Priority: As previously requested in the email from NICE, when updating the model to include TTD from the latest datacut please provide:

a) **Kaplan Meier plot for both arms of the trial including numbers at risk. For talazoparib + enzalutamide please provide for both parts of the combination separately**

b) **Kaplan Meier plot comparing to rPFS including numbers at risk. This can be combined with point a) if this produces a figure which is easy to read**

c) **Consider and justify whether you fit to a combined TTD variable for both parts of the combination or individually to each part of the combination (the latter is likely preferred)**

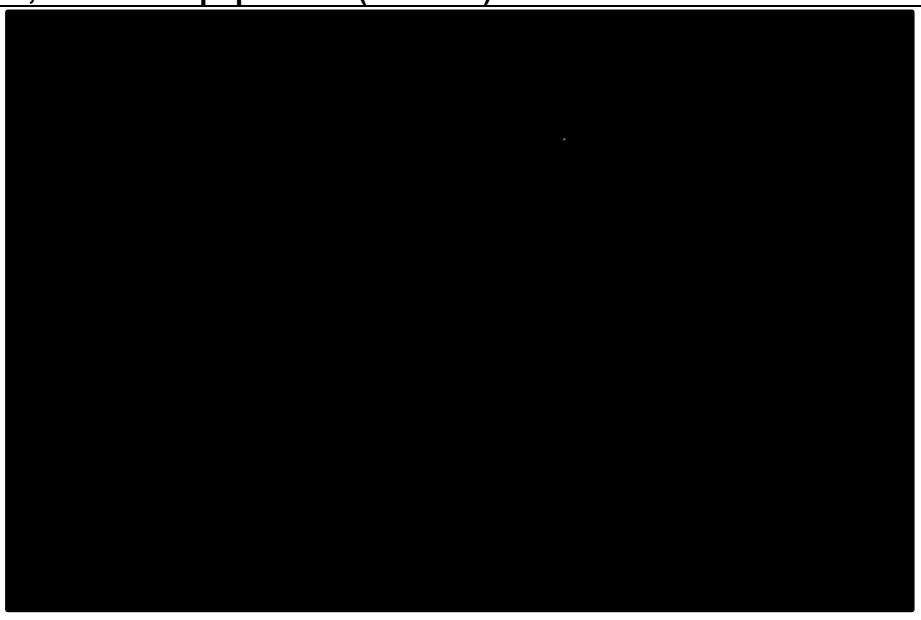
a) The company has now incorporated TTD data for talazoparib with enzalutamide based on the latest data cut of TALAPRO-2 (cutoff date 3rd September 2024). The updated TTD data is now part of the model base case, replacing the previous base case in which TTD was assumed to be equal to rPFS. As agreed with the EAG, unadjusted TTD KMs from TALAPRO-2 have been used.

In line with EAG preference and the approach taken in TA951[1], TTD has been modelled separately for each component of the talazoparib with enzalutamide combination (i.e. separate TTD curves were used for talazoparib and enzalutamide). For each cycle, the lower of the two discontinuation rates (i.e. the higher proportion remaining on treatment) is used to represent the percentage of patients continuing the full combination. This reflects the assumption that drug monitoring requirements are still ongoing if patients remain on either component, and that individual treatment costs continue to accrue until both drugs are discontinued. Figure 7 and Figure 8 display the KM TTD for talazoparib and enzalutamide, respectively, including the numbers at risk.[21]

Figure 7. TTD KM for talazoparib in the talazoparib with enzalutamide arm of TALAPRO-2, all-comers population (cohort 1)

Abbreviations: TTD – Time to discontinuation
Source: Statistical Analysis Report – TALAPRO2 final data cut. Pfizer data on file.[21]

Figure 8. TTD KM for enzalutamide in the talazoparib with enzalutamide arm of TALAPRO-2, all-comers population (cohort 1)



Abbreviations: TTD – Time to discontinuation
Source: Source: Statistical Analysis Report – TALAPRO2 final data cut. Pfizer data on file.[21]

Based on an assessment of statistical fit using AIC and BIC, the log-logistic distribution was selected for both talazoparib and enzalutamide TTD.

Updated base case results using TTD data for talazoparib with enzalutamide are presented in Table 16.

Table 16. Updated base case results, using TTD data for talazoparib with enzalutamide and a pseudo-TTD curve for olaparib with abiraterone

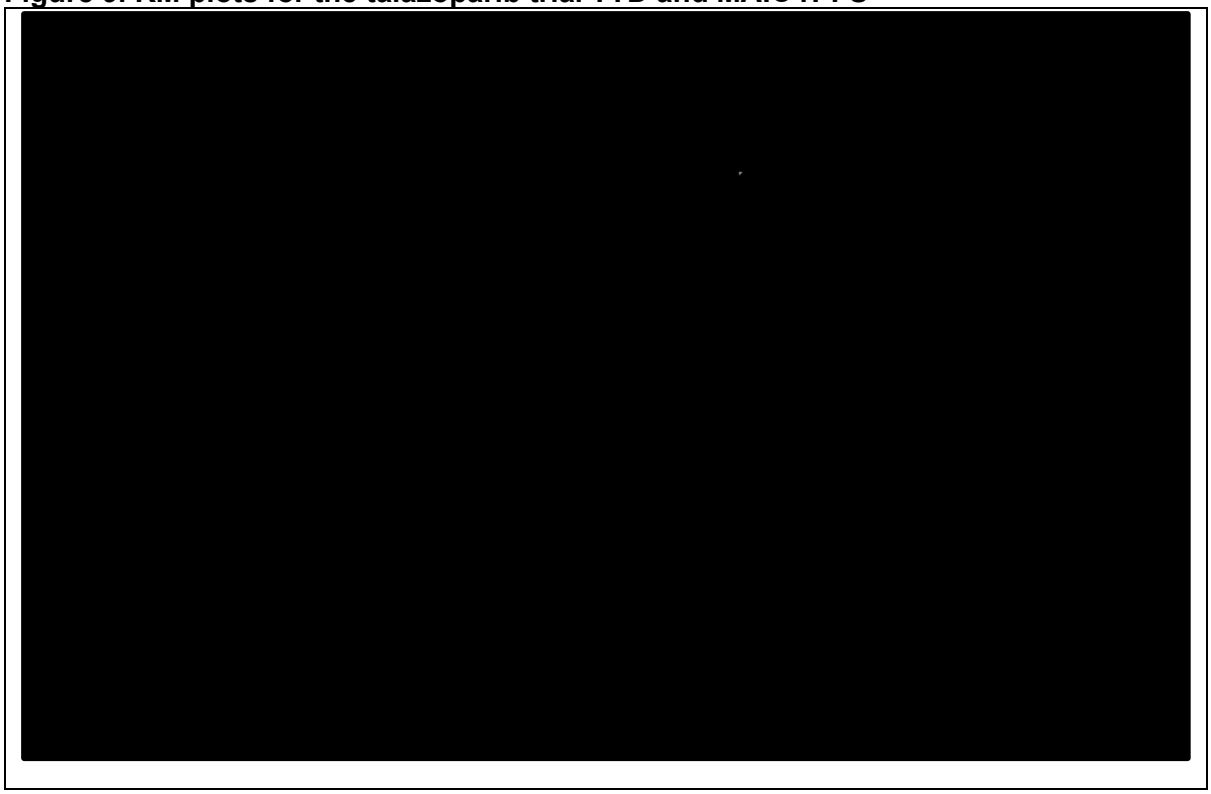
Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

In the absence of TTD KMs for olaparib with abiraterone, the EAG requested, the proportionality between the rPFS and TTD values for the talazoparib with enzalutamide arm be applied to the olaparib with abiraterone rPFS curve in the model as a scenario analysis to calculate a pseudo-TTD curve. However, as presented in Table 15 of the company addendum, there is published evidence demonstrating consistency between TTD and rPFS in PROpel, which supports the assumption that TTD is equal to rPFS for olaparib with abiraterone (data from olaparib CADTH submission[22] and Clarke et al. 2022[4]). Therefore, we do not feel it is appropriate to calculate a pseudo-TTD curve for olaparib with abiraterone.

b) An overlay of KM curves for MAIC rPFS data and the unadjusted TTD data for talazoparib and enzalutamide are presented in Figure 9 and Figure 10, respectively.[21]

Figure 9. KM plots for the talazoparib trial TTD and MAIC rPFS



Abbreviations: AAP – Abiraterone; ENZA – Enzalutamide; MAIC – Matching-adjusted indirect comparison; OLA – Olaparib; rPFS – Radiographic progression free survival; TALA – Talazoparib; TTD – Time to discontinuation.
Source: Source: Statistical Analysis Report – TALAPRO2 final data cut. Pfizer data on file.[21]

Figure 10. KM plots for the enzalutamide trial TTD and MAIC rPFS

Abbreviations: AAP – Abiraterone; ENZA – Enzalutamide; MAIC – Matching adjusted indirect comparison; OLA – Olaparib; rPFS – Radiographic progression free survival; TALA – Talazoparib; TTD – Time to discontinuation
Source: Source: Statistical Analysis Report – TALAPRO2 final data cut. Pfizer data on file.[21]

c) As described in Question B7a), TTD has been modelled separately for each component of the talazoparib with enzalutamide combination.

Skeletal related events

B8. Please justify the inclusion of skeletal related events in the economic model base case given that the cost comparison analysis only included these as a scenario and the concerns raised in the previous EAG report that the evidence was not of sufficient quality to support a differential impact for SREs between treatments

In August 2024, the company consulted with UK clinicians to understand the burden of skeletal related events (SREs). For UK clinicians, spinal cord compression and pain necessitating radiotherapy were the most concerning SREs. Vertebral fractures were also considered another significant concern for patients with mCRPC.

Clinicians acknowledge that the specific percentage of SREs due to either disease progression or osteopenia remains undefined. While SREs may arise from various factors, the prevailing view is that disease progression is considered the dominant contributor. Some fractures are believed to stem from bone health management challenges associated with androgen deprivation therapy (ADT), yet disease progression is typically seen as the primary catalyst. Consequently, clinicians strongly recommend effective prostate cancer management as the optimal strategy to prevent SREs.

In practice, clinicians in the UK offer prophylactic bone protection treatments, such as alendronic acid and calcium, to patients with metastatic castration-resistant prostate cancer (mCRPC) receiving hormone therapy. Although a baseline scan is considered beneficial, it does not impact management strategies for these patients.

Due to the limited survival time and frailty associated with mCRPC, invasive surgeries are generally avoided to reduce the risk of extended hospital stays. Instead, conservative management options like radiotherapy, spinal team consultations, braces, and analgesics are preferred. Although some hospitals may use bone cement in the vertebrae, this approach remains uncommon.

While planning for radiotherapy in SREs is a logistical challenge with minimal impact on NHS resources, spinal cord compression and surgeries for pathological fractures significantly demand healthcare resources and affect patient quality of life.

Therefore, the company decided to incorporate SREs into the economic model base case.

For transparency, we have included results of a scenario analysis, excluding SREs in Table 17.

Table 17. Scenario analysis results, excluding SREs

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Utilities

B9. Priority: Please justify why the health state utilities for progressive disease were taken from TA377 rather than more recent submissions such as TA951. Please demonstrate you have searched for utility data from all appropriate sources and your rationale for selection of this source. The subsequent treatment utilities from this submission appear too low given the majority of patients are expected to receive an active 2nd line treatment in current practice.

We were unable to use health state utilities for progressed disease from TA951[1] as the values are redacted. A targeted search of NICE TAs revealed that TA377[11] was the most recent relevant NICE TA with unredacted progressed disease utility values that could be incorporated into the economic model.

As mentioned in the response to question B1 c), we have identified more recent data from three economic evaluations which have used a value lower than 0.685 (value in our base case from TA377[11]) when modelling the progressed disease health state[14,15,17]; this highlights the conservative approach in our economic base case.

B10. Please report the statistical analysis conducted to derive the utility value of [redacted] used in the progression free health state.

Utility values were calculated for each EQ-5D-5L observation by independently applying the value sets for the UK to the TALAPRO-2 trial data. The EQ-5D-5L to EQ-5D-3L mapping value set developed by the NICE Decision Support Unit (Hernández-Alava and Pudney 2017[23]) was used rather than the specific EQ-5D-5L value set[24], following current NICE guidelines.

Due to the longitudinal nature of the TALAPRO-2 trial, a linear mixed-effects repeated measures model was used to predict EQ-5D utilities for each health state. This type of model allows for repeated measures of EQ-5D utilities for a patient and contains both fixed effects and random effects. Mixed-model analysis provides a general flexible approach in these situations (e.g. in repeated measures) because it allows a wide variety of correlation patterns to be explicitly modelled.[25] These models are a standard approach of utility analysis and, therefore, are familiar to and widely accepted in health technology assessment.

The linear mixed model was applied using HSUVs as the dependent variable, individual patients modelled as random effects, and the following covariates as fixed effects: planned treatment, time of visit (since randomisation), baseline age, baseline HSUV, baseline Eastern Cooperative Oncology Group (ECOG) status, planned treatment, and an interaction term between planned treatment and health state (i.e. pre- and post-progression). As baseline utility was included as a covariate in the regression models, baseline utility observations were excluded from the input dataset. The models predicted HSUVs based on the UK tariffs for each health state within each treatment arm. Marginal HSUV means were derived at the means of the fixed-effects covariates.

The analysis defined the pre-progression health state by observations that occurred before the rPFS event dates. Utility values based on EQ-5D-5L questionnaires collected after the censoring date for rPFS were excluded from the primary analysis as it was unclear which health state patients would be in at the time of assessment.

Table 18 presents the HSUVs estimated from the mixed-effect model for the Cohort 1 (all-comers population) based on the UK value set.[26]

Table 18. Pre-progression marginal mean HSUVs estimated from mixed-effects models: UK value set— All-comers (data cutoff 3rd September 2024)

	Model-Estimated HSUV	
	Mean (SE)	95% CI
Overall sample	[redacted]	[redacted]
TALA + ENZA	[redacted]	[redacted]
PLAC + ENZA	[redacted]	[redacted]

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ENZA = enzalutamide; HSUV = health state utility value; PLAC = placebo; SE = standard error; TALA = talazoparib.
Source: Utility analysis report – TALAPRO-2 final data cut. Pfizer data on file.[26]

Costs and resource use

B11. Priority: When you provide updated RDI information from your updated datacut please provide the information in the format of mean as well as median RDI and per treatment received for intervention and comparator (i.e. separately for both parts of the combination treatment)

Both mean and median RDI estimates from the final data cut of TALAPRO-2 (data cut off 3rd September 2024) for talazoparib with enzalutamide and placebo with enzalutamide have already been presented in Table 5 in the company addendum. Trial participants in TALAPRO-2 could have their talazoparib dose reduced from 0.5mg to either 0.35mg, 0.25mg or 0.1mg (Table 19). Direct application of the mean and median RDI estimates for talazoparib with enzalutamide would not accurately reflect the cost to the NHS in the economic model, given that the dose reduction does not necessarily equate to a price reduction since the list price of the 0.5mg and 0.35mg doses is equal (£3,310) as well as the list price for the 0.25mg and 0.1mg doses (£1,655) (Table 19).

To be able to derive an appropriate RDI estimate which accurately reflects the average talazoparib price across TALAPRO-2 and the cost to the NHS in the economic model, we carried out the following:

1. A post-hoc analysis on trial data to determine the number of participants who receiving each talazoparib dose at the final data cut as well as the mean duration of treatment for each dose (Table 19)

2. Used information derived from the post-hoc analysis to estimate the total proportion of use for each dose throughout TALAPRO 2 (Table 19)

3. Estimated the weighted average price of talazoparib based on the total proportion of use for each dose throughout TALA-PRO 2

We estimated that the weighted average list price of talazoparib throughout TALAPRO-2 was [redacted], which equates to an RDI of [redacted].

Table 19. Post-hoc analysis of dosing exposure of talazoparib - all-comers population (data cutoff 3rd September 2024)

Talazoparib dose (mg)	List price (£)	Number of participants who receiving each dose at final data cut	Mean duration of treatment for each dose (days)	Proportion of total use of dose across entire trial period (%)
0.5	3,310	[redacted]	[redacted]	[redacted]
0.35	3,310	[redacted]	[redacted]	[redacted]
0.25	1,655	[redacted]	[redacted]	[redacted]
0.1	1,655	[redacted]	[redacted]	[redacted]

Source: Pfizer data on file.[27]

Updated base case results including RDI estimates for talazoparib ([redacted]), enzalutamide ([redacted] – median RDI from final data cut of TALAPRO-2, Table 6 in the company addendum), olaparib and abiraterone (98.20% - available median RDI for olaparib with abiraterone combination therapy) are presented in Table 19.

We have also presented the individual impact of adopting the median and mean RDI values for talazoparib and enzalutamide from the final data cut of TALAPRO-2 in Table 20 and Table 21, respectively. As seen from the results in Table 19 to 21, employing our methodology for estimating an appropriate RDI estimate which accurately reflects the average talazoparib price across TALAPRO-2 and the cost to the NHS in the economic model represents a more conservative approach compared to using median or mean RDI values for talazoparib from TALAPRO-2 (final data cut: 3rd September 2024).

The methodology employed to estimate RDI for talazoparib from the final data cut of TALAPRO-2 was validated by UK clinical experts (n=3) who were consulted to help developed responses to the EAG clarification questions (April 2025).

Table 20. Updated base case results, including RDI estimates for talazoparib, enzalutamide, olaparib and abiraterone

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Table 21. Individual impact of including TALARPO-2 median RDI values for talazoparib with enzalutamide and TA951 RDI values for olaparib with abiraterone on the original base case

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Table 22. Individual impact of including TALARPO-2 mean RDI values for talazoparib with enzalutamide and TA951 RDI values for olaparib with abiraterone on the original base case

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

B12. Priority: The costing for oral treatment appears to exclude important costs.

a) **The submitted cost calculations for the oral treatment appear to be based on a per-tablet approach, where the pack cost is divided by the number of tablets and scaled up by the number of tablets taken per days of cycle. However, in NHS practice, oral medicines are typically dispensed in whole packs (or multiple whole packs), and unused pills cannot be returned. Please update the cost calculations to appropriately reflect wastage**

b) **Oral treatments are associated with pharmacy dispensing costs. Please include these in the analysis**

a) Drug wastage for oral therapies, including talazoparib, is already accounted for implicitly in the company base case, by omitting acquisition costs from the half cycle correction. This ensures that, for all patients, the full cost of the planned dose is recognised for all cycles, even when patients discontinue part-way through a cycle. This approach assumes that the exact planned dose is dispensed and used (or wasted) each cycle.

However, a scenario has now been included to explore the assumption that, for oral drugs, only full packs are dispensed, rather than the exact planned dose. In this scenario, each patient is assumed to be allocated only full packs each cycle. Upon discontinuation, the unused doses from the pack(s) are wasted. The scenario assumes that patients discontinue half-way through a cycle, meaning that 50% of a cycle's worth of drug is wasted. For first-line treatments, the cost of these wasted doses are applied when patients transition from the 'rPFS' health state to the 'PDa' health state. In terms of subsequent therapies, the scenario does not account for wastage of prednisolone (the only oral subsequent treatment); this has minimal impact on the model results as any prednisolone wastage incurred after discontinuing talazoparib with enzalutamide would be similar to that following olaparib with abiraterone given that the prednisolone market share is the same for both arms.

Table 23 displays the wastage calculations for the scenario.

Table 23. Wastage calculations for oral drugs (scenario analysis)

Treatment	Packs per cycle	Cost per cycle (£)	Packs wasted at discontinuation	Discontinuation wastage (one-off cost)* (£)
Talazoparib with enzalutamide total	[redacted]	[redacted]	[redacted]	[redacted]
Talazoparib	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone total	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]
Abiraterone acetate	[redacted]	[redacted]	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]	[redacted]	[redacted]

*Applied at point of discontinuation

Results of the scenario analysis, including wastage for oral drugs are presented in Table 24.

Table 24. Scenario analysis results, including wastage for oral drugs

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

b) The base case has been updated to include pharmacy dispensing costs for oral treatments using the "All prescriptions dispensed by English Pharmacy Contractors" Single Activity Fee sourced from the NHS Electronic Drug Tariff website[28], as requested by the EAG. The updated drug costs per cycle are presented in Table 25.

Table 25. Oral drug package price and cost per cycle

Treatment	Dose (mg per unit)	Daily dose (mg)	Pack size	Cost per pack (£)	Administration cost (£)	Cost per cycle (£)	Source
Talazoparib	0.25	0.5	30	[redacted]	1.27	[redacted]	BNF, 2024[29] and NHS Electronic Drug Tariff website[28]
Enzalutamide	40	160	112	2,734.67	1.27	2,963.41	
Olaparib	150	600	56	2,317.50	1.27	4,950.56	
Abiraterone acetate	500	1,000	56	76.91	1.27	166.96	eMIT, 2024[30] and NHS Electronic Drug Tariff website[28]
Prednisolone	5	10	28	0.41	1.27	3.64	

Abbreviations: BNF – British National Formulary; eMIT – Electronic market information tool; mg – Milligram; NHS – National Health Service

Updated base case results including pharmacy dispensing costs for oral treatments are presented in Table 26.

Table 26. Updated base case results, including pharmacy dispensing costs for oral treatments

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

As requested by the EAG, the model has been updated to include the cost of background ADT, assumed to be goserelin (Zoladex) administered via a 30-minute nurse visit for the first dose and self-administered thereafter. Costs are applied monthly.

Updated base case results including background ADT are presented in Table 27.

Table 27. Updated base case results, including background ADT

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

B13. Please justify the large differences in adverse event management costs in the current submission compared to the previous cost comparison analysis. Additionally, please compare the cost codes used to those in TA951

Table 28 presents a comparison of the unit costs and HRG codes for AEs versus the original CS and TA951[1]. Overall, the AE costing methodology is similar across the addendum, original CS, and TA951[1], but with some minor differences.

The AE currency codes used in the addendum are largely consistent with the original CS. The only discrepancy is for anaemia, whereby the addendum also includes currency code SA04L in the cost calculation. The company deemed the use of all five SA04 currency codes appropriate to capture all the potential costs for patients experiencing anaemia symptoms. This approach is consistent with other prostate cancer submissions, such as TA712[31], TA391[32], and TA377[11]. The currency code for all other AEs is the same in both the addendum and the original CS – assumed to be the outpatient (consultant led) service code 370. Differences in AE management costs between the CS and addendum are therefore driven by updated unit costs for each currency code based on the latest available National Schedule of NHS Costs.

A minor error was identified in the cost calculation for anaemia in the addendum and the original CS in which the number of patients costed using each currency code was not accounted for. This has now been corrected using a weighted average of the currency codes SA04G-L, calculated by multiplying the unit cost of each currency code by the number of patients treated under the specific cost category, providing a total cost. The sum of the total costs for each cost category was then divided by the total number of patients to provide a weighted average cost of £612.92.

In TA951[1], the currency codes used for anaemia were SA01G-K which are associated with 'acquired pure red cell aplasia or another aplastic anaemia'. Acquired pure red cell aplasia is a rare autoimmune disorder associated with severe anaemia and is therefore considered an overestimate of the management cost of anaemia. The anaemia currency codes used in the addendum (SA04G-L) are related to 'iron deficiency anaemia', which is more appropriate than TA951 and aligns with the approach taken in previous NICE appraisals in prostate cancer.[11,31,32]

For leukopenia, both the company addendum and TA951[1] assumed an outpatient visit cost. The company sourced this cost from the National Schedule of NHS Costs (2023-24)[33], whereas TA951 uses the PSSRU unit costs of health and social care (2020)[34]. For neutropenia, TA951 applied a cost from TA377.[1,11] The company deemed it more appropriate to maintain the consistent use of the most recent National Schedule of NHS Costs for outpatient visits for any AEs that were not associated with an applicable HRG code. Thrombocytopenia and venous thromboembolic events were not included in TA951.[1]

Table 28. Comparison of adverse event costs versus the original CS and TA951

Adverse event	Addendum		Original CS		TA951	
	Unit cost	Currency code; source	Unit cost	Currency code; source	Unit cost	Currency code; source
Anaemia	[redacted]	Weighted average of SA04G, SA04H, SA04J, SA04K, SA04L: non-elective short stay; National Schedule of NHS Costs (2023/2024)[33]	[redacted]	Weighted average of SA04G, SA04H, SA04J, SA04K: non-elective short stay; National Schedule of NHS Costs (2021-2022) (inflation-adjusted)[35]	£1497.48	Weighted average of SA01G, SA01H, SA01J, SA01K: total HRGs; National Schedule of NHS Costs (2019-2020) (inflation-adjusted)[36]
Leukopenia	[redacted]	Outpatient cost (consultant led); service code 370; National Schedule of NHS Costs (2023/2024)[33]	[redacted]	Outpatient cost (consultant led), service code 370; National Schedule of NHS Costs (2021-2022) (inflation-adjusted)[35]	£139.05	No HRG, assumed same as outpatient visit; PSSRU unit costs of health and social care 2020 (inflation-adjusted)[34]
Neutropenia	[redacted]		[redacted]		£165.83	NA; TA377 (inflation-adjusted)[11]
Thrombocytopenia	[redacted]		[redacted]		NA	NA
Venous thromboembolic event	[redacted]		[redacted]		NA	NA

Abbreviations: AE – Adverse event; NA – Not applicable NHS – National Health Service; PSSRU – Personal Social Services Research Unit

Updated base case results including the correction to the cost of anaemia are presented in Table 29.

Table 29. Updated base case results, including the correction to the cost of anaemia

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

B14. Priority: Please justify the assumption that 65% of time is spent in palliative care rather than on active treatment after talazoparib + enzalutamide. Please provide any clinical opinion you have received on the validity of this assumption as this does not align with the EAG's expectation. If this is not considered realistic on reflection, please revise the economic analysis

To test this assumption, we sought validation from three UK clinical experts (April 2025). We received mixed feedback from UK clinical experts, therefore we have provided scenarios which assume +/-10% of time is spent in palliative care rather than on active subsequent treatment following discontinuation for both treatment arms in the economic model.

Results of the scenario analyses, assuming +10% and -10% of time is spent in palliative care rather than on active subsequent treatment following discontinuation are presented in Table 30 and Table 31, respectively. Overall, varying the time spent in palliative care rather than on active subsequent treatment following discontinuation for both treatment arms has little impact on the updated base case ICER.

Table 30. Scenario analysis results, assuming +10% of time is spent in palliative care vs subsequent treatment

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Table 31. Scenario analysis results, assuming -10% of time is spent in palliative care vs subsequent treatment

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

B15. Priority: The EAG note that abiraterone is now off patent. Is this available for use at 2nd line. If so, please incorporate in the economic analysis

It is possible for a patient to receive abiraterone at the 2nd line in mCRPC provided they are naive to NHT.[37]

However, during the committee discussion in TA951, the clinical lead of NHS England's Cancer Drugs Fund noted that only 40% of individuals with metastatic prostate cancer receive NHT at the time of hormone relapse.[1] This 40% is further divided into two groups: 30% receive NHT as a first-line treatment before chemotherapy is needed, and 10% receive it after undergoing chemotherapy.[1] Furthermore, the EAG report highlighted a statement from the clinical advisor indicating that 90-95% of patients would receive NHT as their treatment, while the remaining patients would undergo chemotherapy.[1] Therefore, option of 2nd line abiraterone will be applicable to only a small proportion of patients.

Retreatment with NHT at the stage of mCRPC is neither recommended by ESMO nor provided by the NHS for patients who have previously received NHT before reaching the mCRPC stages.[2,38] After consultations with three UK clinical experts, there was unanimous agreement that 2nd line treatment with abiraterone is not recommended for patients who have previously been treated with either talazoparib and enzalutamide or olaparib with abiraterone.

In summary, considering all the information provided, the company believes it would be inappropriate to include abiraterone as a 2nd line treatment option in the economic analysis.

B16. Priority: Please provide full information on the original source of the palliative care cost (population, sample size, calculation methods etc…) and how the duration the cost was calculated for in the original source compares to the duration it is applied for within the current economic analysis. The EAG could find no mention of this cost, or any cost being applied other than

subsequent treatments and a one-off cost for terminal care in TA951 so please justify including this additional cost or remove it.

The palliative care cost presented in the addendum was sourced from NICE TA377[11], which based its estimate on Guest et al. 2006[39], a retrospective cohort study in prostate cancer. However, the company acknowledge that this source is outdated and the calculations used to estimate the cost of palliative care in the model are associated with uncertainty. Therefore, the company conducted ad-hoc literature searches to identify relevant alternative sources for palliative care costs. The ad-hoc literature searches identified the Round et al. 2015 paper, which uses a modelling approach to estimate direct and indirect end of life costs for lung, breast, colorectal and prostate cancer in England and Wales.[10] Round et al. 2015 reports a palliative care cost of £9,415 for prostate cancer in the UK, based on both healthcare resource use (e.g., inpatient admissions, outpatient attendances, GP contacts) and social care resource use (e.g., home care, nursing home, residential care; all direct costs sourced from PSSRU).[10] In the SLR, one other relevant cost source was identified (TA387 for abiraterone), which applied a one-off palliative cost of £3,598 to account for the last 3 months of BSC treatment.[40] However, Round et al. 2015 is more reflective of clinical practice due to its direct real-world reporting, and a lack of clarity on the source of the TA387 value.[10,40]

The company have therefore updated the base case to include the palliative care costs from Round et al. 2015.[10] The updated palliative care cost is incorporated into the model by converting the total per-patient cost (£9,415) from Round et al. 2015 into a cost per cycle based on a mean duration of palliative care of 360 days (£1,066.67 per month). The cost was adjusted for inflation to 2024 and applied to patients in the palliative care health state.

The company believe that the inclusion of a palliative care cost is appropriate as it is considered best practice for patients in the UK who are experiencing disease progression and are no longer responding to treatment from second-line therapies (such as docetaxel, radium-223, and cabazitaxel) to receive palliative care.[41] Furthermore, NICE guidance on the treatment and management of patients with metastatic and hormone-relapsed prostate cancer states that palliative interventions should be made available when needed.[42] Clinical expert opinion sought from three

clinical experts in response to EAG clarification questions (April 2025) suggested that the majority of patients receive palliative care, so the removal of this cost from the model would not be appropriate.

Additionally, the company have updated the terminal care cost to £2,300.47 (inflated from 2023 value of £2,170) to align with TA951, as this represents a more recent source than using TA377.[1] This cost is applied as a one-off cost for patients upon death.

Updated base case results using the revised palliative care and terminal care costs are presented in Table 32.

Table 32. Updated base case results, using the palliative care cost from Round et al. 2015 and terminal care cost from TA951

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Validation

B17. Please provide a comparison of the outputs of the economic analysis presented to previous technology appraisals.

Outputs from economic analyses presented in previous relevant technology appraisals, namely TA951 and TA377, are redacted, therefore we are not able to compare outputs.[1,11] We have enquired whether NICE is able to follow up with the submitting company of TA951 and provide redacted outputs for comparison purposes, however, we have not received any correspondence.

Section C: Textual clarification and additional points

C1. Please provide the reference for the source of data for the PROpel TTD KM in Table 15 and comment on whether or not this is the same datacut as the rPFS reported in the Clark et al 2022 paper for rPFS

We can confirm that the source of the data for the PROpel TTD KM in Table 15 in the company addendum is from the Clarke et al. 2022[4] publication (data cutoff: 30th July 2021).

Additional Clarification Questions

The company reported on the all-comers population in Cohort 1 of TALAPRO-2. However, the company did continue enrolment in TALAPRO-2 (Cohort 2) where it was restricted to people with HRR gene alterations. The efficacy and safety data for Cohort 2 were not reported in the CS or in the addendum.

1. How do the efficacy and safety data at the latest datacut in Cohort 2 compare with efficacy and safety data at a similar timepoint in Cohort 1?

2. Please can you comment on expected effect of using Cohort 2 rather than Cohort 1 on the cost-effectiveness estimates?

1. The company would like to clarify that the reason efficacy and safety data from Cohort 2 were not included in the addendum was because we are not looking for a NICE recommendation in this patient population, but rather the all-comers population in Cohort 1 (similar to TA951[1]). It is imperative to underscore that in the UK, talazoparib has received its license for use in combination with enzalutamide specifically for the treatment of adult patients with mCRPC for whom chemotherapy is deemed clinically inappropriate, regardless of their mutational status.[43] This approval is firmly based on the data from TALAPRO-2 Cohort 1.[43] However, for transparency, we have included these data below from the final data cut of TALAPRO-2 (data cutoff date: 3rd September 2024).

   Primary efficacy endpoint: BICR assessed rPFS

   A descriptive analysis of rPFS per blinded independent central review (BICR) was conducted based on the final OS cutoff date (3rd September 2024) for the Cohort 2 TALAPRO-2 population. As presented in Table 33 and Figure 11, the analysis demonstrated the clinically meaningful improvement was maintained with talazoparib plus enzalutamide over placebo plus enzalutamide, with a 53.2% reduction in the risk of disease progression or death in the talazoparib plus enzalutamide arm compared with the placebo plus enzalutamide arm.[44]

   The observed stratified HR (talazoparib plus enzalutamide versus placebo plus enzalutamide) was 0.468 (95% CI: 0.359, 0.612; 1-sided p<0.0001).[44] At this

descriptive analysis, median rPFS has been reached for both arms. Median rPFS was 30.7 (95% CI: 24.3, 38.5) months for participants who received talazoparib plus enzalutamide and was 12.3 (95% CI: 11.0, 16.5) months for participants who received placebo plus enzalutamide.[44]

The probability of being event-free at 24 months was [redacted] for participants who received talazoparib plus enzalutamide and [redacted] for participants who received placebo plus enzalutamide.[44]

Median duration of follow up for BICR assessed rPFS was [redacted] months for participants who received talazoparib plus enzalutamide and [redacted] months for participants who received placebo plus enzalutamide.[44]

Table 33. TALAPRO-2: Summary of BICR-assessed rPFS for Cohort 2 - ITT Part 2 DDR-deficient population at final data cutoff 3rd September 2024 (N=399)

	Talazoparib with enzalutamide (n=200)	Placebo with enzalutamide (n=199)	Hazard ratio (95% CI)	2-sided p-value
Median rPFS by BICR, months (95% CI)[a]	30.7 (24.3, 38.5)	12.3 (11.0, 16.5)	0.468 (0.359, 0.612)	<0.0001
Events (%)	99 (49.5)	127 (63.8)	--	--
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	--	--
24 months	[redacted]	[redacted]	--	--
36 months	[redacted]	[redacted]	--	--
48 months	[redacted]	[redacted]	--	--

[a] Based on the Brookmeyer-Crowley method.
[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.
Abbreviations: BICR – Blinded independent central review; CI – Confidence interval; DDR – DNA damage repair; ITT – Intention-to-treat; rPFS – Radiographic progression-free survival
Source: TALAPRO-2 1.0 Interim Cohort 2 CSR – Table 15. Pfizer data on file.[44]

Figure 11. Kaplan-Meier plot of BICR assessed rPFS - ITT Part 2 DDR-deficient population (Cohort 2 – data cutoff 3rd September 2024)

Abbreviations: BICR - blinded independent central review; CI – confidence interval; DDR – DNA damage repair; HR – hazard ratio; ITT – intention to treat; rPFS – radiographic progression-free survival.
Source: TALAPRO-2 1.0 Interim Cohort 2 CSR – Figure 3. Pfizer data on file.[44]

Key secondary endpoint: OS

As of the final OS cutoff date (3rd September 2024), at which time 219 events had occurred, there was a clinically meaningful and statistically significant improvement in OS in favour of participants treated with talazoparib plus enzalutamide compared with placebo plus enzalutamide. There was a 37.8% reduction in the risk of death compared with the placebo plus enzalutamide arm.[44]

The observed stratified HR was 0.622 (95% CI: 0.475, 0.814; 1-sided p=0.0002) in favour of participants treated with talazoparib plus enzalutamide (Figure 12), representing 37.8% reduction in the risk of death compared with the placebo plus enzalutamide arm.[44] The median OS based on Kaplan-Meier method was 45.1 (95% CI: 35.4, NE) months for participants who received talazoparib plus enzalutamide, and 31.1 (95% CI: 27.3, 35.4) months for participants who received placebo plus enzalutamide.[44]

The probability of survival at 36 months was [redacted] for participants who received talazoparib plus enzalutamide and [redacted] for participants who received placebo plus enzalutamide.[44] Median duration of follow-up for OS was 44.2 months for participants who received talazoparib plus enzalutamide and 44.4 months for participants who received placebo plus enzalutamide.[44]

Figure 12. Kaplan-Meier plot of OS - ITT Part 2 DDR-deficient population (Cohort 2 – data cutoff 3rd September 2024)

Abbreviations: BICR - blinded independent central review; CI – confidence interval; DDR – DNA damage repair; HR – hazard ratio; ITT – intention to treat; rPFS – radiographic progression-free survival.
Source: TALAPRO-2 1.0 Interim Cohort 2 CSR – Figure 5. Pfizer data on file.[44]

Safety

All Grade and Grade 3 or greater adverse events (AEs) were reported more frequently in the talazoparib with enzalutamide treatment arm compared with the placebo plus enzalutamide treatment arm.[44]

The most frequently reported AEs (occurring in >20% of participants) in the talazoparib plus enzalutamide treatment arm included anaemia (66.7%), neutrophil count decreased and fatigue (34.8% each), platelet count decreased (25.8%), back pain (24.2%), decreased appetite (23.2%), hypertension (22.2%) and nausea and white blood cell count decreased (21.7%) each.[44]

The most frequent AEs (occurring in >20% of participants) in the placebo plus enzalutamide treatment arm included arthralgia (24.6%), fatigue (28.1%), back pain (23.1%), and constipation (20.6%).[44]

Treatment-related AEs are summarised in Table 34.[44]

Table 34. Summary of Treatment-Emergent Adverse Events by Preferred Term and CTCAE Grade (All Grade and Grade 3 or greater) Experienced by ≥10% of Participants - Safety Cohort 2 DDR-Deficient Population

Number of Participants Evaluable for AEs	Talazoparib + Enzalutamide (N=198)			Placebo + Enzalutamide (N=199)		
Number (%) of Participants by Preferred Term	**All Grade n (%)**	**Grade ≥ 3 n (%)**	**Total n (%)**	**All Grade n(%)**	**Grade ≥ 3 n (%)**	**Total n (%)**
With Any Adverse Event	186 (93.9)	125 (54.0)	186 (93.9)	179 (89.9)	35 (17.6)	179 (89.9)
Anaemia	132 (66.7)	86 (43.4)	132 (66.7)	37 (18.6)	9 (4.5)	37 (18.6)
Fatigue	69 (34.8)	3 (1.5)	69 (34.8)	56 (28.1)	2 (1.0)	56 (28.1)
Neutrophil count decreased	69 (34.8)	39 (19.7)	69 (34.8)	14 (7.0)	2 (1.0)	14 (7.0)
Platelet count decreased	51 (25.8)	15 (7.6)	51 (25.8)	5 (2.5)	1 (0.5)	5 (2.5)
Back pain	48 (24.2)	3 (1.5)	48 (24.2)	46 (23.1)	3 (1.5)	46 (23.1)
Decreased appetite	46 (23.3)	2 (1.0)	46 (23.3)	31 (15.6)	2 (1.0)	31 (15.6)
Hypertension	44 (22.2)	22 (11.1)	44 (22.2)	39 (19.6)	16 (8.0)	39 (19.6)
Nausea	43 (21.7)	3 (1.5)	43 (21.7)	36 (18.1)	1 (0.5)	36 (18.1)
White blood cell count decreased	43 (21.7)	14 (7.1)	43 (21.7)	15 (7.5)	0	15 (7.5)
Fall	39 (19.7)	5 (2.5)	39 (19.7)	28 (14.1)	3 (1.5)	28 (14.1)
Asthenia	34 (17.2)	5 (2.5)	34 (17.2)	33 (16.6)	0	33 (16.6)
Arthralgia	33 (16.7)	1 (0.5)	33 (16.7)	49 (24.6)	0	49 (24.6)
Constipation	32 (16.2)	0	32 (16.2)	41 (20.6)	0	41 (20.6)
Diarrhoea	27 (13.6)	0	27 (13.6)	24 (12.1)	0	24 (12.1)
Hot flush	24 (12.1)	0	24 (12.1)	33 (16.6)	0	33 (16.6)
Pyrexia	22 (11.1)	1 (0.5)	22 (11.1)	4 (2.0)	0	4 (2.0)
Dizziness	21 (10.6)	1 (0.5)	21 (10.6)	16 (8.0)	2 (1.0)	16 (8.0)
Weight decreased	21 (10.6)	4 (2.0)	21 (10.6)	18 (9.0)	1 (0.5)	18 (9.0)
Dyspnoea	20 (10.1)	1 (0.5)	20 (10.1)	11 (5.5)	0	11 (5.5)
Headache	14 (7.1)	0	14 (7.1)	24 (12.1)	1 (0.5)	24 (12.1)

MedDRA v27.0 coding dictionary applied. CTCAE version 4.03 criteria have been used.
The denominator to calculate percentages is N, the number of participants in the safety analysis set within each treatment group.

Participants reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For participants reporting more than one AE within a system organ class or preferred term, the AE with maximum grade is included in the table.
The treatment emergent period is from first dose through 28 days after the last dose of study treatment, or before new systemic (i.e. not including surgery or radiotherapy) antineoplastic therapy, whichever occurs first.
Source: TALAPRO-2 1.0 Interim Cohort 2 CSR – Table 27. Pfizer data on file.[44]

2. As mentioned in our response to Additional Question 1, we are not looking for a NICE recommendation in Cohort 2 but rather Cohort 1, in line with the talazoparib with enzalutamide license for use in the UK, and therefore we have not conducted any cost-effectiveness analyses in this patient population.

The following publication is what we understand to be the/a relevant MAIC conducted by Pfizer: Castro E, Wang D, Walsh S, Craigie S, Haltner A, Nazari J, Niyazov A, Samjoo IA. Talazoparib plus enzalutamide versus olaparib plus abiraterone acetate and niraparib plus abiraterone acetate for metastatic castration-resistant prostate cancer: a matching-adjusted indirect comparison. Prostate Cancer Prostatic Dis. 2024 Dec 7. doi: 10.1038/s41391-024-00924-x. Epub ahead of print. PMID: 39645562. https://pubmed.ncbi.nlm.nih.gov/39645562/

The MAIC analysis mentioned above was conducted using a prior data cut from TALAPRO-2 (data cutoff date: 28th March 2023 for OS and 16th August 2022 for all other outcomes).[45] The results from this MAIC are superseded by those from the more recently conducted MAIC in the company addendum, as the analysis was conducted using the final data cut from TALAPRO-2 (data cutoff date: 3rd September 2024).

This is a query not specifically related to the clarification meeting but is of interest to us for the appraisal. The following poster is a source of a portion of the utility data used by the company in the model: https://ascopubs.org/doi/10.1200/jco.2012.30.5_suppl.240 However, we cannot access this poster, and it was not provided by the company in the submission. Please can you ask the company to send a copy of the poster which we understand to be the source of the utility data.

The company was not able to locate the associated poster either and have not received any correspondence from NICE regarding the contents of the poster.

References

1. NICE. TA951. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. https://www.nice.org.uk/guidance/ta951/resources/olaparib-with-abiraterone-for-untreated-hormonerelapsed-metastatic-prostate-cancer-pdf-82615723963333
2. Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Sep 2020;31(9):1119-1134. doi:10.1016/j.annonc.2020.06.011
3. Agarwal N, Azad AA, Carles J, et al. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet*. Jul 22 2023;402(10398):291-303. doi:10.1016/s0140-6736(23)01055-3
4. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. *NEJM Evid*. Sep 2022;1(9):EVIDoa2200043. doi:10.1056/EVIDoa2200043
5. Pfizer. TALAPRO-2 1.0 Interim All-comers CSR. Data on File;
6. de Bono JS, Smith MR, Saad F, et al. Subsequent Chemotherapy and Treatment Patterns After Abiraterone Acetate in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. *Eur Urol*. Apr 2017;71(4):656-664. doi:10.1016/j.eururo.2016.06.033
7. Beer TM, Armstrong AJ, Rathkopf D, et al. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol*. Feb 2017;71(2):151-154. doi:10.1016/j.eururo.2016.07.032
8. Armstrong AJ, Lin P, Higano CS, et al. Development and validation of a prognostic model for overall survival in chemotherapy-naïve men with metastatic castration-resistant prostate cancer. *Ann Oncol*. Nov 1 2018;29(11):2200-2207. doi:10.1093/annonc/mdy406
9. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. (Technical Support Documents). NICE Decision Support Unit. 2016;
10. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med*. Dec 2015;29(10):899-907. doi:10.1177/0269216315595203
11. NICE. TA377. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. https://www.nice.org.uk/guidance/ta580/documents/committee-papers
12. Rathkopf DE, Roubaud G, Chi KN, et al. Patient-reported Outcomes for Patients with Metastatic Castration-resistant Prostate Cancer and BRCA1/2 Gene Alterations: Final Analysis from the Randomized Phase 3 MAGNITUDE Trial. *Eur Urol*. Sep 23 2024;doi:10.1016/j.eururo.2024.09.003
13. Kuzma M, Nekvindova L, Kliment J. Quality of life for androgen receptor targeted agents in patients with metastatic castration resistant prostate cancer. *Bratisl Lek Listy*. 2024;125(9):572-579. doi:10.4149/bll_2024_89
14. Duru E, Mattingly TJ, Malone DC. Cost-Effectiveness of Niraparib Plus Abiraterone Acetate and Prednisone for Metastatic Castration-Resistant Prostate Cancer. *Value in Health*. 2024;27(6)(S1)

15. Zeng X, Liu Q, Tan C, Wan X, Wang Y, Ma X. Alpha emitter radium-223 in patients with metastatic castration-resistant prostate cancer: A cost-utility analysis. *Front Pharmacol*. 2022;13:1003483. doi:10.3389/fphar.2022.1003483
16. Tirado Mercier E, Callejo Velasco D, Rubio Cabezas M, Moretones Agut C, Granell Villalón M. Cost-effectiveness Analysis of Radium-223 Dichloride in Metastatic Castration-Resistant Prostate Cancer Patients Without Previous Chemotherapy Treatment in Spain. *J Health Econ Outcomes Res*. 2018;6(1):1-14. doi:10.36469/9777
17. Goudarzi Z, Lotfi F, Najafpour Z, Hafezi A, Zakaria MA, Keshavarz K. Cost-effectiveness and budget impact analysis of enzalutamide in comparison to abiraterone in treatment of metastatic prostate cancer resistant to castration in Iran. *BMC Urol*. Feb 20 2024;24(1):45. doi:10.1186/s12894-024-01431-w
18. Okumura H, Inoue S, Naidoo S, Holmstrom S, Akaza H. Cost-effectiveness analysis of enzalutamide for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer in Japan. *Jpn J Clin Oncol*. Aug 1 2021;51(8):1319-1329. doi:10.1093/jjco/hyab071
19. Hagiwara Y, Shiroiwa T, Shimozuma K, et al. Impact of Adverse Events on Health Utility and Health-Related Quality of Life in Patients Receiving First-Line Chemotherapy for Metastatic Breast Cancer: Results from the SELECT BC Study. *Pharmacoeconomics*. Feb 2018;36(2):215-223. doi:10.1007/s40273-017-0580-7
20. Latimer NR. Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data: Inconsistencies, Limitations, and a Practical Guide. *Medical Decision Making*. 2013/08/01 2013;33(6):743-754. doi:10.1177/0272989X12472398
21. Pfizer. PRJ000396: Survival Analysis and Extrapolation of the Final TALAPRO-2 Data for Talazoparib in Metastatic Castration-Resistant Prostate Cancer. Statistical Analysis Report. Data on file. 2025;
22. CADTH Reimbursement Reviews and Recommendations. *Olaparib (Lynparza): CADTH Reimbursement Recommendation: Indication: In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated BRCA mutation must be confirmed before olaparib treatment is initiated*. Canadian Agency for Drugs and Technologies in Health; 2024.
23. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. *J Health Econ*. Sep 2017;55:139-152. doi:10.1016/j.jhealeco.2017.06.013
24. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Economics*. 2018/01/01 2018;27(1):7-22. doi:https://doi.org/10.1002/hec.3564
25. Zhang X, Zou G, Liang H. Model averaging and weight choice in linear mixed-effects models. *Biometrika*. 2014;101(1):205-218. doi:10.1093/biomet/ast052
26. Pfizer. PRJ000396: Estimating Utility Values in mCRPC Using the Final TALAPRO-2 Data for Cohort 1 (All-Comers) and Cohort 2 (HRRm and BRCAm). Data on file. 2025;

27. Pfizer. Dosing Exposure of Talazoparib - Safety Part 2 All-comers Population. Protocol C344102.
28. NHS. NHS Electronic Drug Tariff. https://www.drugtariff.nhsbsa.nhs.uk/#/00885392-DC/DC00885322/Part%20IIIA%20-%20Professional%20Fees%20(Pharmacy%20Contractors)
29. BNF. Drugs A to Z I BNF content published by NICE. https://bnf.nice.org.uk/drugs
30. Drugs and pharmaceutical electronic market information tool (eMIT). GOV.UK. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit
31. NICE. TA712. Enzalutamide for treating hormone-sensitive metastatic prostate cancer. https://www.nice.org.uk/guidance/ta712/evidence/committee-papers-pdf-9191003869
32. NICE. TA391. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. https://www.nice.org.uk/guidance/ta391/evidence/appraisal-consultation-committee-papers-pdf-10888998445
33. NHS. National Schedule of NHS Costs (2023-2024). https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/
34. PSSRU. Unit Costs of Health and Social Care. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/
35. NHS. National Schedule for NHS costs (2021-2022). https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/
36. NHS. National Schedule of NHS Costs (2019-2020). https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/
37. NICE. TA259. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. https://www.nice.org.uk/guidance/ta259
38. NICE. TA887. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer. https://www.nice.org.uk/guidance/ta887/chapter/3-Committee-discussion
39. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur J Cancer Care (Engl)*. Mar 2006;15(1):65-73. doi:10.1111/j.1365-2354.2005.00623.x
40. NICE. TA387. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. https://www.nice.org.uk/guidance/ta387/resources/abiraterone-for-treating-metastatic-hormonerelapsed-prostate-cancer-before-chemotherapy-is-indicated-pdf-82602854745541
41. Prostate Cancer UK. Prostate Cancer UK's Best Practice Pathway. https://prostatecanceruk.org/media/zwoenyz4/5741-best-practice-pathway_update_june19_v5.pdf
42. NICE. Prostate cancer: diagnosis and management I Guidance. https://www.nice.org.uk/guidance/ng131
43. Pfizer Ltd. Talzenna 0.25 mg hard capsules: Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/10734/smpc

44. Pfizer. TALAPRO-2 1.0 Interim Cohort 2 CSR. Data on file.
45. Castro E, Wang D, Walsh S, et al. Talazoparib plus enzalutamide versus olaparib plus abiraterone acetate and niraparib plus abiraterone acetate for metastatic castration-resistant prostate cancer: a matching-adjusted indirect comparison. *Prostate Cancer Prostatic Dis*. Dec 7 2024;doi:10.1038/s41391-024-00924-x
46. Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. PERFORMANCE OF OVID MEDLINE SEARCH FILTERS TO IDENTIFY HEALTH STATE UTILITY STUDIES. *Int J Technol Assess Health Care*. Jan 2017;33(4):472-480. doi:10.1017/s0266462317000897

Appendix

1. Literature search for HRQoL data in mCRPC

Date of the search: 18th November 2024

Databases searched:

- Ovid MEDLINE®
- Ovid MEDLINE Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily
- Ovid Embase
- Ovid EBM Reviews - Cochrane Central Register of Controlled Trials

Search strategy

#	Searches
1	Prostatic Neoplasms/ or (((prostate or prostatic) adj3 (adenocarcinoma$ or adeno-carcinoma$ or cancer$ or carcinoma$ or malignan$ or neoplas$ or tumor? or tumour?)) or PC or PCa).ti,ab,kf.
2	Orchiectomy/ and (insensitiv$ or refractor$ or resistan$).ti,ab,kf.
3	(((androgen? or castrat$ or hormon$) adj2 (independen$ or insensitiv$ or refractor$ or resistan$)) or ((orchectom$ or orcheotom$ or orchidectom$ or orchiectom$ or testectom$ or (removal adj3 (testicle? or test#s))) and (insensitiv$ or refractor$ or resistan$))).ti,ab,kf.
4	1 and (2 or 3)
5	Prostatic Neoplasms, Castration-Resistant/ or (MCRPC or CRPC or MCRPCa or CRPCa or (((prostate or prostatic) adj3 (adenocarcinoma$ or adeno-carcinoma$ or cancer$ or carcinoma$ or malignan$ or neoplas$ or tumor? or tumour?)) and ((androgen? or castrat$ or hormon$) adj2 (independen$ or insensitiv$ or refractor$ or resistan$)))).ti,ab,kf.
6	4 or 5
7	exp Animals/ not Humans/
8	6 not 7 [ANIMAL-ONLY REMOVED]
9	(comment or editorial or news or newspaper article).pt.
10	(letter not (letter and randomized controlled trial)).pt.
11	8 not (9 or 10) [OPINION PIECES REMOVED]
12	Quality-Adjusted Life Years/
13	(quality adjusted or adjusted life year$).ti,ab,kf.
14	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kf.
15	(illness state$1 or health state$1).ti,ab,kf.
16	(hui or hui1 or hui2 or hui3).ti,ab,kf.
17	(multiattribute$ or multi attribute$).ti,ab,kf.
18	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf.
19	utilities.ti,ab,kf.
20	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).ti,ab,kf.
21	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf.
22	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf.
23	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf.
24	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf.

25	quality of life/ and ec.fs.
26	quality of life/ and (health adj3 status).ti,ab,kf.
27	(quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/
28	or/12-27 [Arber 2017 Utilities filter - balanced]
29	("European Quality of Life questionnaire 5D" or "disability adjusted life" or "sickness impact profile" or daly$ or (short form 36 or shortform 36 or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D) or (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or (hql or hqol or h qol or hrqol or hr qol) or (hye or hyes) or health$ year$ equivalent$ or disutili$ or rosser or (quality adj2 wellbeing) or qwb or standard gamble$).ti,ab. or (SG and gamble).ab. [ADDITIONAL TERMS TO SUPPLEMENT Arber 2017 Utilities filter]
30	28 or 29
31	11 and 30 [(m)CRPC & MEDLINE Utilities filter Arber2017 - balanced]
32	**31 use ppez [MEDLINE records]**
33	exp prostate cancer/ or (((prostate or prostatic) adj3 (adenocarcinoma$ or adeno-carcinoma$ or cancer$ or carcinoma$ or malignan$ or neoplas$ or tumor? or tumour?)) or PC or PCa).ti,ab,kw.
34	orchiectomy/ and (insensitiv$ or refractor$ or resistan$).ti,ab,kw.
35	(((androgen? or castrat$ or hormon$) adj2 (independen$ or insensitiv$ or refractor$ or resistan$)) or ((orchectom$ or orcheotom$ or orchidectom$ or orchiectom$ or testectom$ or (removal adj3 (testicle? or test#s))) and (insensitiv$ or refractor$ or resistan$))).ti,ab,kw.
36	33 and (34 or 35)
37	castration resistant prostate cancer/ or (MCRPC or CRPC or MCRPCa or CRPCa or (((prostate or prostatic) adj3 (adenocarcinoma$ or adeno-carcinoma$ or cancer$ or carcinoma$ or malignan$ or neoplas$ or tumor? or tumour?)) and ((androgen? or castrat$ or hormon$) adj2 (independen$ or insensitiv$ or refractor$ or resistan$)))).ti,ab,kw.
38	36 or 37
39	exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/
40	exp human/ or exp human experimentation/ or exp human experiment/
41	39 not 40
42	38 not 41 [ANIMAL-ONLY REMOVED]
43	editorial.pt.
44	letter.pt. not (letter.pt. and randomized controlled trial/)
45	42 not (43 or 44) [OPINION PIECES REMOVED]
46	Quality-Adjusted Life Year/
47	(quality adjusted or adjusted life year$).ti,ab,kw.
48	(qaly$ or qald$ or qale$ or qtime$).ti,ab,kw.
49	(illness state$1 or health state$1).ti,ab,kw.
50	(hui or hui1 or hui2 or hui3).ti,ab,kw.
51	(multiattribute$ or multi attribute$).ti,ab,kw.
52	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw.
53	utilities.ti,ab,kw.
54	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).ti,ab,kw.
55	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw.
56	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw.
57	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.

58	"quality of life"/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.
59	"quality of life"/ and ec.fs.
60	"quality of life"/ and (health adj3 status).ti,ab,kw.
61	(quality of life or qol).ti,ab,kw. and "cost benefit analysis"/
62	or/46-61 [Arber 2017 Utilities filter - balanced]
63	exp "European Quality of Life 5 Dimensions questionnaire"/ or exp "Short Form 36"/ or ("European Quality of Life questionnaire 5D" or "disability adjusted life" or "sickness impact profile" or daly$ or (short form 36 or shortform 36 or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D) or (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or (hql or hqol or h qol or hrqol or hr qol) or (hye or hyes) or health$ year$ equivalent$ or disutili$ or rosser or (quality adj2 wellbeing) or qwb or standard gamble$).ti,ab. or (SG and gamble).ab. [ADDITIONAL TERMS TO SUPPLEMENT Arber 2017 Utilities filter]
64	62 or 63
65	45 and 64 [(m)CRPC & Embase Utilities filter Arber2017 - balanced]
66	conference abstract.pt.
67	65 not 66 [CONFERENCE ABSTRACTS REMOVED]
68	65 and 66
69	limit 68 to yr="2016 -Current" [MOST RECENT 5 YEARS CONF ABSTRACTS RETAINED]
70	67 or 69
71	**70 use oemezd [Embase results]**
72	Prostatic Neoplasms/ or (((prostate or prostatic) adj3 (adenocarcinoma$ or adeno-carcinoma$ or cancer$ or carcinoma$ or malignan$ or neoplas$ or tumor? or tumour?)) or PC or PCa).ti,ab,kw.
73	Orchiectomy/ and (insensitiv$ or refractor$ or resistan$).ti,ab,kw.
74	(((androgen? or castrat$ or hormon$) adj2 (independen$ or insensitiv$ or refractor$ or resistan$)) or ((orchectom$ or orcheotom$ or orchidectom$ or orchiectom$ or testectom$ or (removal adj3 (testicle? or test#s))) and (insensitiv$ or refractor$ or resistan$))).ti,ab,kw.
75	72 and (73 or 74)
76	Prostatic Neoplasms, Castration-Resistant/ or (MCRPC or CRPC or MCRPCa or CRPCa or (((prostate or prostatic) adj3 (adenocarcinoma$ or adeno-carcinoma$ or cancer$ or carcinoma$ or malignan$ or neoplas$ or tumor? or tumour?)) and ((androgen? or castrat$ or hormon$) adj2 (independen$ or insensitiv$ or refractor$ or resistan$)))).ti,ab,kw.
77	75 or 76
78	Quality-Adjusted Life Years/
79	(quality adjusted or adjusted life year$).mp.
80	(qaly$ or qald$ or qale$ or qtime$).mp.
81	(illness state$1 or health state$1).mp.
82	(hui or hui1 or hui2 or hui3).mp.
83	(multiattribute$ or multi attribute$).mp.
84	(utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).mp.
85	utilities.mp.
86	(eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or European qol).mp.
87	(euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).mp.
88	(sf36$ or sf 36$ or sf thirtysix or sf thirty six).mp.
89	(time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).mp.
90	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).mp.

91	quality of life/ and ec.fs.
92	quality of life/ and (health adj3 status).mp.
93	Cost-Benefit Analysis/ and (quality of life or qol).mp.
94	or/78-93 [Arber 2017 Utilities filter - balanced]
95	("European Quality of Life questionnaire 5D" or "disability adjusted life" or "sickness impact profile" or daly$ or (short form 36 or shortform 36 or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or (sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D) or (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or (hql or hqol or h qol or hrqol or hr qol) or (hye or hyes) or health$ year$ equivalent$ or disutili$ or rosser or (quality adj2 wellbeing) or qwb or standard gamble$).ti,ab. or (SG and gamble).ab. [ADDITIONAL TERMS TO SUPPLEMENT Arber 2017 Utilities filter]
96	94 or 95
97	77 and 96 [(m)CRPC & CENTRAL Utilities filter Arber et al. 2017[a] - balanced]
98	**97 use cctr**
99	32 or 71 or 98
100	**remove duplicates from 99 [All databases - deduplicated]**

[a] Utility filters from Arber et al 20217[46].

PICOS criteria for the SLR of HRQoL evidence

	Inclusion Criteria	Exclusion Criteria
Population	Study populations or subgroups of patients (humans only; men) with: • Age ≥ 18 years • Histologically or cytologically confirmed adenocarcinoma of the prostate • Undergone surgical or medical castration • Metastatic disease[a] • Castration-resistant/Hormone-resistant/Hormone-refractory/Androgen-independent prostate cancer • Asymptomatic or mildly symptomatic mCRPC[a,b,c] • Treatment naïve in the mCRPC setting[a,b]	Study populations or subgroups: • Non-human • Age <18 years • No surgical castration or medical castration • Non-metastatic disease • Non-CRPC • Hormone-sensitive disease • Any previous systemic cancer treatment for mCRPC disease state[d]
Interventions	Any treatments available or under investigation for mCRPC provided as a single-agent or a combination treatment[e]	Those not listed in *Inclusion Criteria*
Comparators	Any treatments available or under investigation for mCRPC provided as a single-agent or a combination treatment[e], or BSC, placebo, or watchful waiting	Those not listed in *Inclusion Criteria*
Outcomes	• Generic preference-based HSUVs from the following instruments: o EQ-5D-3L o EQ-5D-5L o SF-6D o HUI3 o QWB index o 15D o AQoL • Generic measures from the following instruments: o SF-36 • Disease-specific measures from the following instruments: o EORTC QLQ-C30 o EORTC QLQ-PR25 o FACT-G o FACT-P • Values generated by measures which might be mapped on to the EQ-5D that are not already included above • Mapping algorithms of measurement instruments used in mCRPC to derive HSUVs	Those not listed in *Inclusion Criteria*
Study Design	• RCTs irrespective of blinding status • Non-RCTs • Observational studies (eg, registry studies, prospective and retrospective cohort studies, cross-sectional studies) • Any HSUV elicitation studies (eg, TTO, SG, VAS) • Economic evaluations: o cost-effectiveness studies o cost-utility studies • Conference abstracts • Assessment from HTA agencies where full reviewer's reports are available	• Pre-clinical studies • Pharmacokinetic studies • Case study, series, or reports • Expert opinion articles • Letters • Editorials • Narrative (non-systematic) reviews • Pilot studies • Protocols • SLRs[f]
Language[g]	Articles in English	All non-English articles
Dates	Databases: inception-present Conference abstracts: 2019-present	Databases: none Conference abstracts: prior to 2019

[a] Search strategy will not be limited to metastatic disease, by line of treatment, or severity of disease; however, studies reporting solely non-metastatic patients will be excluded during the screening phase.

[b] The primary population of interest will be asymptomatic or mildly symptomatic patients who are treatment naïve; however, patients with later-line mCRPC and/or moderately/severely symptomatic disease may be considered as a secondary population depending on the availability of data for the primary population of interest.
[c] The definition of symptomatic disease will not be restricted, and definitions based on pain and/or other symptoms will be included. Differing definitions will be evaluated at the feasibility assessment stage.
[d] Androgen deprivation therapy is not exclusionary.
[e] Treatments under investigation for mCRPC include, but are not limited to, PARP inhibitors, chemotherapy agents, immunotherapies, NHTs, radiotherapy, ipatasertib etc.
[f] Relevant SLRs will not be included in the final included studies list; however, their bibliographies will be reviewed for any additional relevant studies.
[g] Search strategy will not be limited by language; however, non-English articles will be excluded during the screening phase.
Abbreviations: 15D = 15-dimensional; AQoL = Assessment of Quality of Life; BSC = best supportive care; CRPC = castration-resistant prostate cancer; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; EORTC QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Prostate Cancer Module; EQ-5D = EuroQuol 5-Dimension; EQ-5D-3L = EuroQuol 5-Dimension 3-Level; EQ-5D-5L = EuroQuol 5-Dimension 5-Level; FACT-G = Functional Assessment of Cancer Therapy-General; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HSUVs = health-state utility values; HTA = Health Technology Assessment; HUI3 = health utilities index mark 3; mCRPC = metastatic castration-resistant prostate cancer; PARP = poly (ADP-ribose) polymerase; QWB = Quality of Well-Being; RCT = randomized controlled trials; SF-36 = 36-Item Short Form Health Survey; SF-6D = Short-Form Six-Dimensions; SG = standard gamble; SLR = systematic literature review; TTO = time trade-off; VAS = visual analogue scale.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

Fractional polynomials network meta-analysis – response to EAG clarification question A6

May 2025

File name	Version	Contains confidential information	Date
ID4004_Prostate talazoparib clarification question A6_FP NMA_28MAY25_[noCON]	1.0	No	28th May 2025

Contents

Tables and figures

Abbreviations

AAP	Abiraterone acetate
CEM	Cost-effectiveness model
CrI	Credible interval
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
KM	Kaplan Meier
LY	Life year
MAIC	Matching adjusted indirect comparison
NMA	Network meta-analysis
OLAP	Olaparib
OS	Overall survival
PH	Proportional hazards
PLD	Patient level data
QALY	Quality-adjusted life year
rPFS	Radiographic progression-free survival

Executive Summary

The EAG for ID4004 asked Pfizer to address the below priority clarification question (A6):

Please conduct an indirect treatment comparison using an anchored approach, such as fractional polynomials, to address non-proportional hazards. This can be conducted either with or without adjustment for potential confounding treatment effect modifiers if you believe these to be an issue.

To address this question, we performed a fractional polynomial (FP) network meta-analysis (NMA) to estimate the comparative efficacy of radiographic progression-free survival (rPFS) and overall survival (OS) for olaparib with abiraterone acetate (OLAP + AAP) versus talazoparib with enzalutamide (TALA + ENZA). The FP NMA does not rely on the proportional hazard assumption and can produce time-varying hazard ratios (HRs) for OLAP + AAP versus TALA + ENZA that can be applied to the TALA + ENZA rPFS and OS extrapolations to estimate the rPFS and OS for OLAP + AAP.

In the updated cost-effectiveness model (CEM) to implement the FP NMA results (ID4004_Prostate talazoparib clarification question A6_FP NMA CEM_28MAY25_CON), parametric survival models for TALA + ENZA rPFS and OS fitted to the unadjusted Kaplan-Meier (KM) data from TALAPRO-2 study were implemented so that the time-varying HRs can be applied. The rPFS and OS for TALA + ENZA rPFS and OS were chosen as log-normal and generalised gamma, respectively, aligning with the updated MAIC base case described in our responses to EAG's questions shared on 24th April 2025 (ID4004_Prostate talazoparib clarification questions_24APR25_[CON]).

The FP NMA is based on a network including four studies (TALAPRO-2, PROpel, NCT02294461 and COU-AA-302) and five interventions (TALA + ENZA, ENZA, OLAP + AAP, AAP and best supportive care [BSC]). Patient-level data were used for TALA + ENZA and ENZA in the TALAPRO-2 study and digitized data from published rPFS and OS KM data for other studies. No formal feasibility assessment including the assessment of potential confounding treatment effect modifiers were performed due to time constraints.

Seven first-order and 28 second-order FP models were fitted. All second-order rPFS and OS FP models had convergence issues and were deemed not appropriate to inform the comparative efficacy in the CEM. All first-order OS FP models also either had convergency issues or very wide credible intervals (CrIs) likely due to the small network and NCT02294461 study having short (<20 months) OS KM data follow-up. First-order rPFS models with p=-1, -0.5 and 0 had reasonable convergence and CrIs, and were therefore deemed suitable for implementation in the CEM. First-order rPFS FP model with p=-1 was chosen as the most plausible FP scenario as it has the best statistical fit based on DIC; other suitable models (p=-0.5 and 0) can be tested as scenarios by changing the model settings.

Considering no FP model was deemed suitable for OS, and that the proportional hazards (PH) assumption appears to hold (see our response to EAG's priority clarification question A4 shared on 24th April 2025), we used time-constant OS HRs for OLAP + AAP versus TALA + ENZA based on standard anchored NMA (both random-effects with HR=1.36 [95% CrI, 0.30, 13.18] and fixed-effects with HR=1.13 [95% CrI, 0.80, 1.61]) and based on MAIC (HR=1.20; 95% CrI, 0.95-1.52). The HR based on the MAIC approach was chosen as the base case as we believe MAIC is the most suitable approach to establish comparative efficacy between TALA + ENZA and OLAP + AAP given the evidence base as we argued in the original and updated base case CEM ("ID14004_Talazoparib_mCRPC_CEM_11MAR25_CON.xlsb" and "ID4004_Prostate talazoparib clarification questions_CEM_24APR25_CON.xlsb") where the comparative efficacy was also based on the MAIC approach (though applied by fitting independent parametric survival models to MAIC adjusted TALA + ENZA KM data and digitised OLAP+AAP KM data from PROpel).

The estimated rPFS and OS extrapolations for OLAP + AAP in this most plausible FP scenario (i.e. time-varying rPFS HR using first-order FP model with p=-1 and time-constant OS HR based on MAIC, both applied to TALA + ENZA rPFS and OS based on unadjusted TALARPO-2 patient-level data) are below the reported KM data in the PROpel study, especially for rPFS. These differences are expected because the HRs (either from FP NMA or MAIC) are applied to the TALA + ENZA rPFS and OS based on unadjusted patient-level data from TALAPRO-2, therefore the model prediction for rPFS and OS for OLAP + AAP is essentially for patients in the TALAPRO-2 study as

if they receive OLAP + AAP (which is expected to be different compared with patients in PROpel study receiving OLAP + AAP). Therefore, we do not regard the differences between modelled rPFS and OS for OLAP + AAP and observed rPFS and OS KM for OLAP + AAP in PROpel study as concerns for the approach.

In summary, the most plausible FP scenario applied time-varying HRs based on the first-order FP rPFS model with p=-1 and a constant HR based on MAIC and these HRs were applied to the TALA + ENZA rPFS and OS based on parametric survival models (log-normal for rPFS and generalised gamma for OS) fitted to the unadjusted KM data from the TALAPRO-2 study. The deterministic CEM results for this most plausible FP scenario are presented in Table 1, which predicts more LY and QALY gains ([redacted] and [redacted], respectively) for TALA + ENZA versus OLAP + AAP compared with the updated MAIC base case results ([redacted] and [redacted], respectively).

Table 1. TALA+ENZA vs. OLAP + AAP most plausible FP scenario deterministic base case

Technologies	Total			Incremental			ICER per QALY (£)	INMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FP, fractional polynomial; ICER – incremental cost-effectiveness ratio; INMB – incremental net monetary benefit; LYG – life-years gained; mCRPC – metastatic castration-resistant prostate cancer; OLAP + AAP – olaparib with abiraterone acetate; QALYs – quality-adjusted life years; TALA+ENZA – talazoparib with enzalutamide.

The most plausible FP scenario predicts TALA + ENZA has [redacted] less undiscounted LYs post progression versus OLAP + AAP (see Table 9) suggesting significantly worse post-progression survival for TALA + ENZA, which lacks face validation given the feedback from clinical experts that the post-progression survival should be the same for OLAP + AAP and TALA + ENZA when both regimens have the same subsequent treatments (which is the assumption in the CEM). Therefore, we have also performed an exploratory surrogate analysis where the OS for TALA + ENZA and OLAP + AAP was estimated by applying a HR of [redacted] (95% CrI, [redacted]) to the rPFS for TALA + ENZA and OLAP + AAP, respectively, where the HR was estimated as the HR of OS versus rPFS using patient-level data in the TALA + ENZA arm in TALAPRO-2. This

exploratory analysis yields even greater LY and QALY gains ([redacted], respectively) and, as expected, similar post-progression survival for TALA + ENZA versus OLAP + AAP compared with the most plausible FP scenario.

In conclusion, FP NMA generated some plausible first-order models and time-varying HRs for rPFS for OLAP + AAP versus TALA + ENZA but did not provide suitable results for OS. Instead, the time-constant OS HR based on MAIC was used. These HRs were applied to the TALA + ENZA rPFS and OS parametric survival models fitted to the unadjusted patient-level data in the TALAPRO-2 study. The most plausible FP scenario predicts more LY and QALY gains compared with the updated MAIC base case; and the results are even more favourable for TALA + ENZA in the exploratory surrogate analysis.

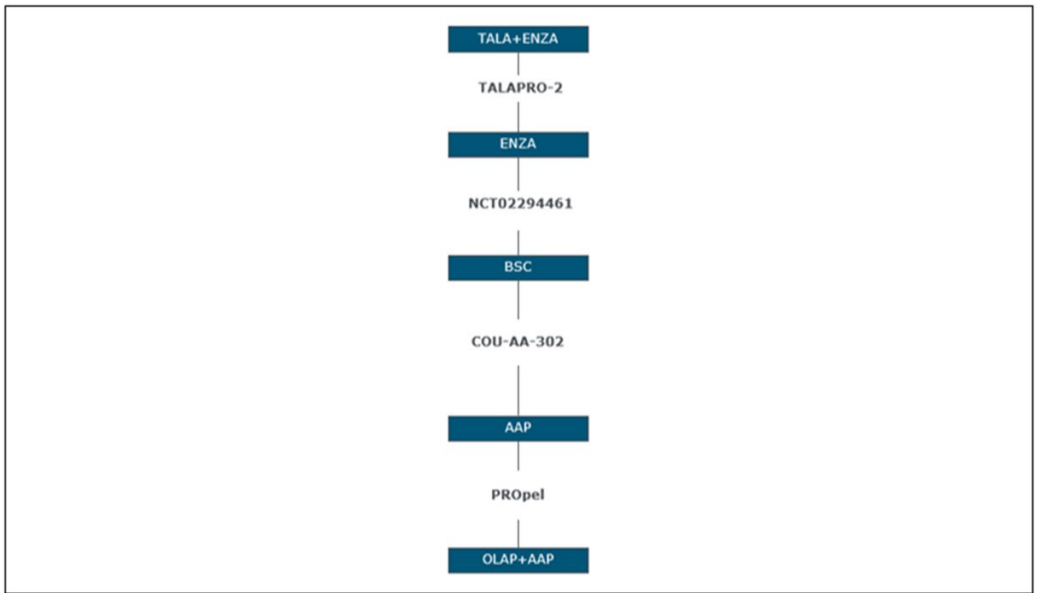
In conclusion, due to the high degree of uncertainty in results from the FP NMA due to the small network and likely short follow-up for the NCT02294461 study, ***the company's updated MAIC base case which uses independent parametric models*** fitted to PROpel and TALAPRO-2 MAIC adjusted KM data (please see full description of the updated MAIC base case in our responses to EAG clarification questions shared on 24 April 2025) ***is considered to be most appropriate for decision-making***.

Fractional polynomial network meta-analysis

Network

FP NMA was conducted on a small evidence base, to inform the indirect treatment comparison for OS and rPFS between TALA + ENZA (talazoparib and enzalutamide) and OLAP + AAP (Olaparib and abiraterone acetate + prednisone/prednisolone) (Figure 1). These analyses require patient level data (PLD) or pseudo PLD from all studies included in the network. Kaplan Meier data from three comparator studies, PROpel, COU-AA-302 and NCT02294461, were digitised and PLD from the TALAPRO-2 study were used to generate the FP NMA models for the networks. The PREVAIL study, which compares ENZA to BSC was not included in the network as Kaplan Meier data was not published, however the comparison between ENZA and BSC was still possible as NCT02294461 explored the same comparison and intervention.

Figure 1. OS and rPFS network (n= 5 interventions, n = 4 studies)



Abbreviations: AAP – abiraterone acetate PO QD 1000 mg + prednisone/prednisolone 5 mg PO BID/10 mg PO QD; BSC – best supportive care (placebo, prednisone 5 mg PO BID, hydrocortisone 40 mg PO QD, and prednisolone 5 mg PO BID); ENZA – enzalutamide 160 mg PO QD; OLAP, Olaparib 300 mg PO BID; OS – overall survival; rPFS – radiographic progression-free survival; TALA – talazoparib 0.5 mg QD.

Methodology

FP NMA model selection was based on the visual fit to the published KM graphs, statistical parsimony based on deviance information criterions (DICs), biological

plausibility, and model diagnostics such as density and trace plots. Models which reached convergence were considered better fit than those without convergence with lower statistical parsimony, models without convergence were deemed not suitable to be implemented into the CEM. Due to the small network size and varying follow-up times of studies included in the network, model convergence was anticipated to be an issue for the network. Random effects models were not conducted as there is only a single study informing each treatment comparison in the network, and the estimation of between-trial standard deviation was not expected to be reliable.

FP NMAs capture multi-dimensional treatment effect by removing the PH restriction where the transitivity assumption holds (trial populations and study settings are sufficiently similar). All treatments are assumed to follow the same polynomial functional form (within the same set of pre-specified power terms) for their baseline hazard, with differences captured by treatment-specific coefficients. This model type requires choice of power for first and potentially second-order exponents in the time varying model. The use of second shape parameters permits change in hazards ratio over time, flexible to fit various forms of observed data. However, convergence is especially hard to achieve in 2nd-order FP models, results can be sensitive to the chosen powers and may overfit if an overly complex polynomial is selected, especially in networks with sparse data.

Aggregated data with time, number of events and number of censoring events are used as data input for the FP NMA, where typically results suggest that the implementation of shorter time-interval improves fitting. For the networks generated in this analyses, time intervals of 0.5 months were used, in which it was generally assumed the proportional hazards assumption holds.

For both outcomes, the following model parameters were explored:

- Seven first-order fixed effects models with the following p1 values: -2, -1, -0.5, 0 , 0.5, 1, 2.
- Twenty-eight second-order fixed effects models, with distinct first and second-order polynomial values from -2, -1, -0.5, 0 , 0.5, 1, 2.

For the purposed of replicability of results, the following R files have been shared describing the functions generated for implementing the FP NMA methodology:

- 1. Source function – Data formatting.R
- FP source code.R

All statistical output is generated through a Bayesian framework and utilizes the fractional polynomial functions from gemtcPlus, an R statistical software package that provides models and functions for fitting FP models from pseudo PLD.

The files which create the data frames with the evidence base used to generate the network of interest for both OS and rPFS are shared, with the following file names:

- 1a. Data formatting for FPs_OS.R
- 1b. Data formatting for FPs_rPFS.R
- 1c. Pseudo PLD csv files.zip

These files utilize the pseudo PLD generated from KM digitisations for each arm in NCT02294461, COU-AA-302 and PROpel and PLD from the TALAPRO-2 study. The PLD from the TALAPRO-2 stud can be shared upon request.

The scripts which generate the analyses, for both OS and rPFS first and second order fixed effects models explored:

- 2a. Specifying FP NMAs inputs 1st order_OS.R
- 3ai. Specifying FP NMAs inputs 2nd order_OS_1Ocoeff-2to0.R
- 3aii. Specifying FP NMAs inputs 2nd order_OS. 1Ocoeff0.5to2.R
- 2b. Specifying FP NMAs inputs 1st order_rPFS.R
- 3bi. Specifying FP NMAs inputs 2nd order_rPFS.R

Notably, due to time constraints of running the second-order fractions polynomial models, the OS second-order codes were split up into 2 scripts so they can be on separate computers simultaneously, one executing second-order polynomial values from -2, -1, -0.5 and 0 (3ai. Specifying FP NMAs inputs 2nd order_OS_1Ocoeff-

2to0.R) and one executing second-order polynomial values from 0.5, 1 and 2 (3bi. Specifying FP NMAs inputs 2nd order_rPFS.R).

Results

Model selection and convergence issues

For both OS and rPFS, 3 chains were generated in the Bayesian FP NMA model, n = 300,000 iterations were run with a burn-in of n = 150,000 and a thinning of 30. These values were selected in attempt to reach convergence.

Table 2 shows the convergence summary for FP models.

Table 2. Convergence Summary

Model	Exponents	OS Convergence inspection	Conclusion	rPFS Convergence inspection	Conclusion
1st order	-2	Highly autocorrelated in most parameters; extremely poor mixing shown in density plot for some parameters; wide CrIs on survival found in some treatments	Poor	Autocorrelation found in some parameters; poor mixing shown in density plot for some parameters; wide CrIs on survival found in some treatments	Weak
	-1	Highly autocorrelated in most parameters; mixing not well shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Weak	Low autocorrelation in all parameters; acceptable mixing shown in density plot for all parameters; wide CrIs on survival found in some treatments	Acceptable
	-0.5	Highly autocorrelated in most parameters; mixing not well shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Weak	Low autocorrelation in all parameters; acceptable mixing shown in density plot for all parameters; comparatively narrow CrIs on survival across treatments	Acceptable
	0	Highly autocorrelated in most parameters; mixing not well shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Weak	Low autocorrelation in all parameters; acceptable mixing shown in density plot for all parameters; comparatively narrow CrIs on survival across treatments	Acceptable
	0.5	Highly autocorrelated in most parameters; extremely poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor	Autocorrelation found in some parameters; poor mixing shown in density plot for some parameters; wide CrIs on survival found in some treatments	Weak
	1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all	Poor	Highly autocorrelated in some parameters; poor mixing shown in density plot for all	Poor

Model	Exponents	OS Convergence inspection	Conclusion	rPFS Convergence inspection	Conclusion
		parameters; very wide CrIs on survival found in some treatments		parameters; very wide CrIs on survival found in some treatments	
	2	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
2nd order	-2, -2	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for most parameters; very wide CrIs on survival found in some treatments	Poor
	-2, -1	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for most parameters; very wide CrIs on survival found in some treatments	Poor
	-2, -0.5	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for most parameters; very wide CrIs on survival found in some treatments	Poor
	-2, 0	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for most parameters; very wide CrIs on survival found in some treatments	Poor
	-2, 0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor

Model	Exponents	OS Convergence inspection	Conclusion	rPFS Convergence inspection	Conclusion
	-2, 1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-2, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-1, -1	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-1, -0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-1, 0	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-1, 0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in most parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-1, 1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor

Model	Exponents	OS Convergence inspection	Conclusion	rPFS Convergence inspection	Conclusion
	-1, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-0.5, -0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in some parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor
	-0.5, 0	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; wide CrIs on survival found in some treatments	Poor
	-0.5, 0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-0.5, 1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	-0.5, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	0, 0	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; wide CrIs on survival found in some treatments	Poor

Model	Exponents	OS Convergence inspection	Conclusion	rPFS Convergence inspection	Conclusion
	0, 0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Weak	Highly autocorrelated in most parameters; poor mixing shown in density plot for some parameters; wide CrIs on survival found in some treatments	Poor
	0, 1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; wide CrIs on survival found in some treatments	Poor
	0, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor
	0.5, 0.5	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; wide CrIs on survival found in some treatments	Poor
	0.5, 1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor
	0.5, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor
	1, 1	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for all parameters; very wide CrIs on survival found in some treatments	Poor

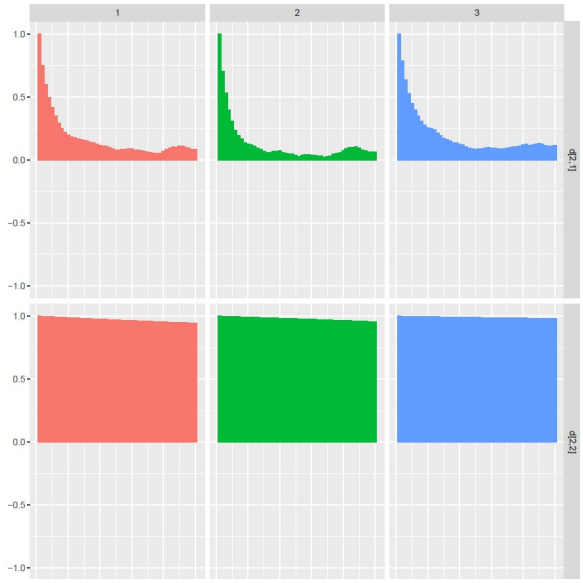
Model	Exponents	OS Convergence inspection	Conclusion	rPFS Convergence inspection	Conclusion
	1, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor
	2, 2	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor	Highly autocorrelated in all parameters; poor mixing shown in density plot for some parameters; very wide CrIs on survival found in some treatments	Poor

Abbreviations: CrIs – credible intervals; OS – overall survival; rPFS – radiographic progression-free survival.
Note: Model in orange represents a weak model, and model in green represents an acceptable model.

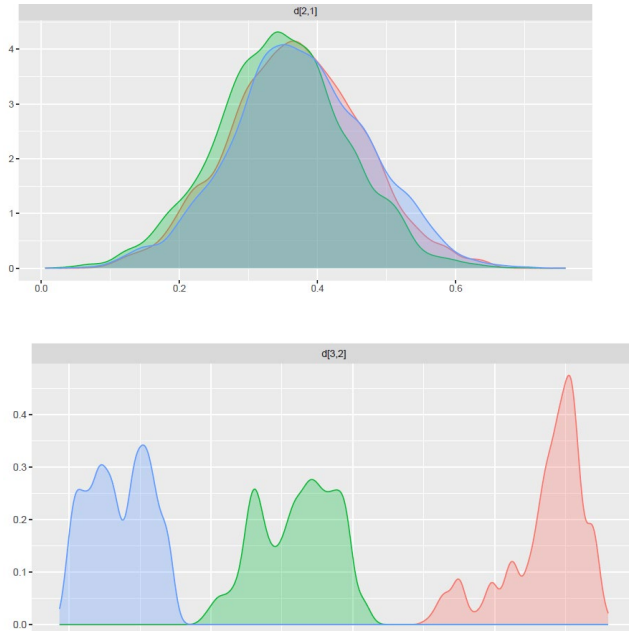
Overall, we found that no models achieved acceptable convergence for OS, which was likely due to immaturity of data for NCT02294461 trial. For example, as illustrated in Figure 2, the first-order model with P1 = -2 exhibited significant autocorrelation in several parameters. The density plot revealed both acceptable and extremely poorly mixed posterior parameter estimates. Additionally, the CrIs for the survival estimates were notably wide in some treatment such as BSC (Figure 2 [C]), indicating unreliable estimates which would lead to implausible survival extrapolation.

Figure 2. Convergence inspection (OS P1=-2 model)

(A) Auto-correlation plot



(B) Density plot



(C) Survival plot

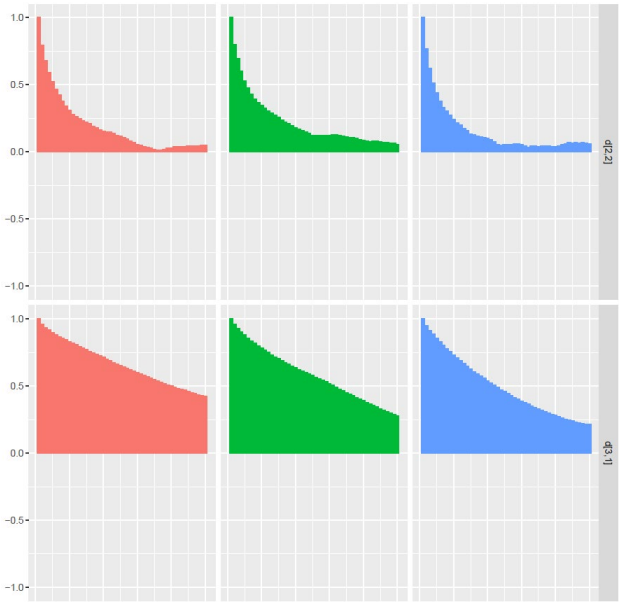
Abbreviations: AAP – abiraterone acetate + prednisone/prednisolone; BSC – best supportive care; ENZA, enzalutamide; OLAP – olaparib; OS – overall survival; TALA – talazoparib.

Note: Only the most and the least suitable estimates based on model convergence were presented for demonstration.

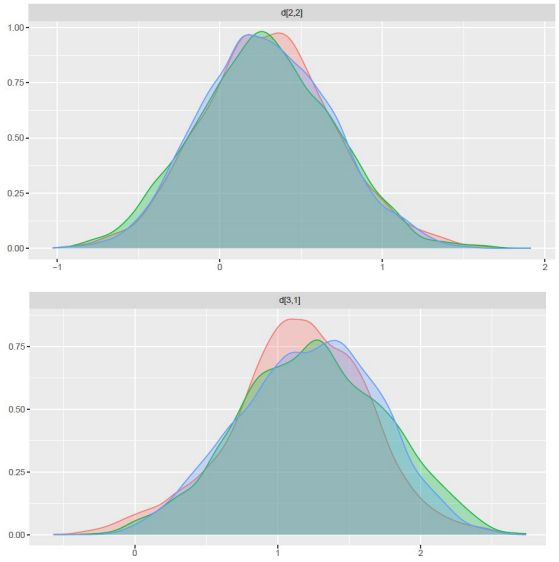
On the other hand, limited models converged for rPFS. It was shown acceptable convergence for several 1st-order models (P1 = -1, -0.5, 0). In Figure 3, as demonstrated in the P1=-0.5 model, low autocorrelation, well mixing of sampling in density plot, and reasonable width of CrI in survival plot suggested an acceptable convergence of such model.

Figure 3. Convergence inspection (rPFS P1=-0.5 model)*

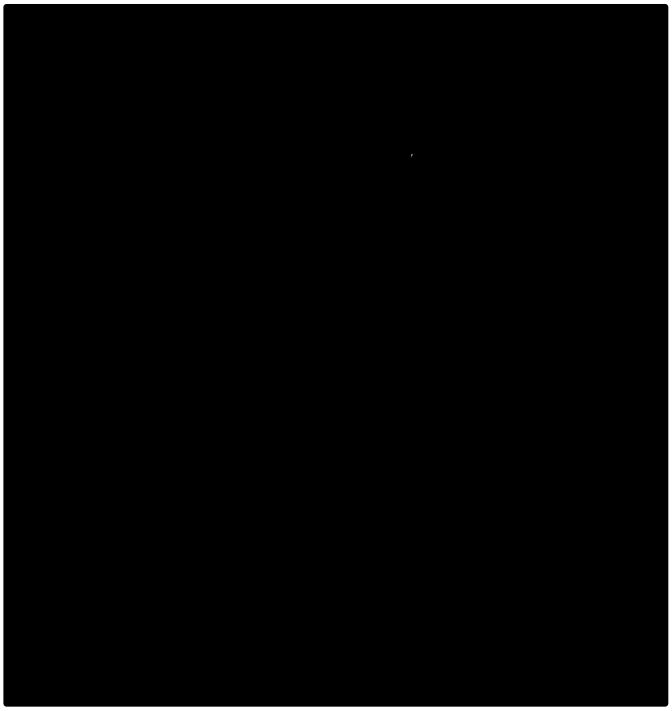
(A) Auto-correlation plot



(B) Density plot



(C) Survival plot



*Only the most and least suitable estimates based on model convergence were presented for demonstration.
Abbreviations: AAP – abiraterone acetate + prednisone/prednisolone; BSC – best supportive care; ENZA – enzalutamide; OLAP – olaparib; rPFS – radiographic progression-free survival; TALA – talazoparib.
.

Across both OS and rPFS, none of the 2nd order FP NMA models converged. Convergence issues were likely due to the small network, with only one trial informing each comparison and the lack of follow-up for NCT02294461 trial. ***Attachment 1*** and ***Attachment 2*** included the complete list of convergence diagnostic plots for all models.

- *Attachement 1: Convergence plots – OS*
- *Attachement 2: Convergence plots – rPFS*

OS

It was found that no FP NMA models achieved acceptable convergence, hence estimates derived from FP NMA were deemed inappropriate for decision-making.

rPFS models with acceptable convergence

As discussed in Model selection and convergence issues section, a few first-order FP NMA models had acceptable convergence (p1 = -1, -0.5, 0). The DIC statistics are shown in Table 3, in which p1=-1 are with the lowest DIC suggesting potentially the best-fitted model.

Table 3. DIC table (rPFS 1st order FP NMA models)

Model	Exponents	DIC
1st order	-2	NE
	-1*	3589.1
	-0.5*	3639.5
	0*	3683.5
	0.5	3696.8
	1	3694.2
	2	3694.1

*Only models with acceptable convergence (P1= -1, -0.5, 0) are considered in model selection.
Abbreviations: DIC – deviance information criterion; NE – not estimable; rPFS – radiographic progression-free survival.

The KM overlay plots in Figure 4 suggested the investigated three models fitted well to the COU_AA_302, NCT02294461 and PROpel trial data, however, all fail to capture the end tail of TALAPRO_2 trial data. In Figure 5 similar point estimates were found in the three models, with the P1=0 include most narrow CrI on survival. Uncertainty around

survival estimates of AAP and OLAP + AAP is highest in the P1 = -1 model. These survival estimates were obtained directly from the NMA model using TALAPRO-2 as the reference trial, which serve as a validity check for the CEM survival estimates. It is important to note that these estimates will not match the CEM survival estimates precisely due to the differing baseline curves used in each analysis. The HR estimates provided in Figure 6 and with 95% CrIs also suggested that similar treatment effects were estimated from these three models, with wider 95% CrIs identified in the P1=0 model.

Figure 4. Kaplan-Mier curves overlayed with estimated survival plots - rPFS

(A) P1=-1

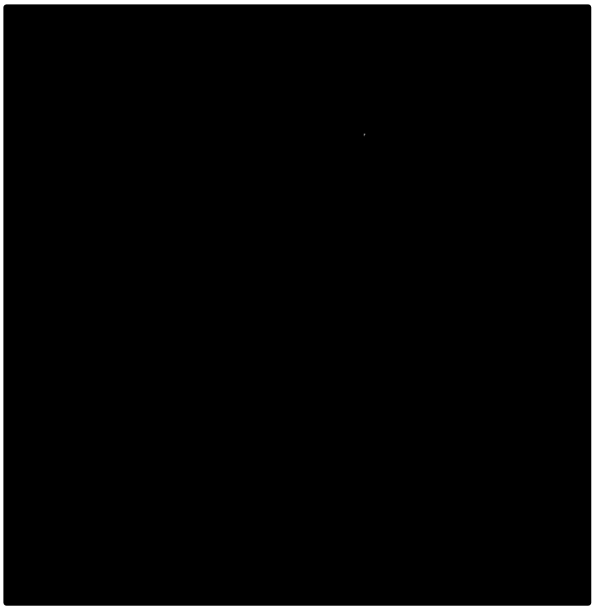
(B) P1=-0.5

(C) P1=0

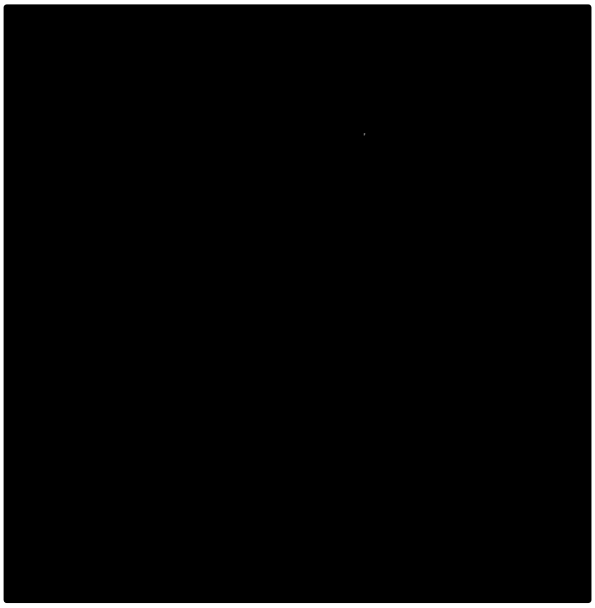
Abbreviations: AAP – abiraterone acetate + prednisone/prednisolone; BSC – best supportive care; ENZA – enzalutamide; OLAP – olaparib; rPFS – radiographic progression-free survival; TALA – talazoparib.
Note: KM plots are only shown for the most suitable models based on converged estimate.

Figure 5. Survival plots - rPFS

(A) P1=-1



(B) P1=-0.5



(C) P1=0

Abbreviations: AAP – abiraterone acetate + prednisone/prednisolone; BSC – best supportive care; ENZA – enzalutamide; OLAP – olaparib; rPFS – radiographic progression-free survival; TALA – talazoparib.

Note: Survival plots are only shown for the most suitable models based on converged estimate.

Figure 6. HRs plots (treatments versus TALA+ENZA)- rPFS

(A) P1=-1

(B) P1=-0.5

(C) P1=0

Abbreviations: AAP – abiraterone acetate + prednisone/prednisolone; BSC – best supportive care; ENZA – enzalutamide; OLAP – olaparib; rPFS – radiographic progression-free survival; TALA – talazoparib.
Note: HR plots are only shown for the most suitable models based on converged estimate.

Implementation in cost-effectiveness analysis

TALA + ENZA clinical effectiveness

The updated MAIC base case relied on standard parametric curves fit to MAIC adjusted KM data for TALA + ENZA. As HRs from the FP NMAs are derived using unadjusted TALA + ENZA KM data, it was necessary to use unadjusted TALA + ENZA KM data to extrapolate OS and rPFS for these scenarios. The rPFS and OS for TALA + ENZA were chosen as log-normal and generalised gamma, respectively, aligning with the updated MAIC base case. The resulting landmark survival estimates for TALA + ENZA are presented in Table 4.

Table 4. Landmark survival estimates for TALA + ENZA using extrapolations of unadjusted and MAIC adjusted KM data

Year	rPFS (log normal)		OS (generalised gamma)	
	MAIC adjusted KM	Unadjusted KM	MAIC adjusted KM	Unadjusted KM
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: KM – Kaplan-Meier; MAIC, matching-adjusted indirect treatment comparison; OS – overall survival; rPFS – radiographic progression free survival; TALA + ENZA – talazoparib with enzalutamide.

OLAP + AAP rPFS

Due to the concerns around convergence in some of the models, mentioned above, only three first-order rPFS models (*p=-1, p=-0.5 and p=0*) were selected for implementation in the CEM. Based on statistical fit to the data and visual inspection of the HR over time (Figure 7), the *p=-1* first-order curves were selected for rPFS, as the most appropriate alternative source of relative effectiveness data for OLAP + AAP.

Figure 7. rPFS time-varying HRs: OLAP + AAP vs. TALA+ENZA

Abbreviations: HR – hazard ratio; OLAP + AAP – olaparib with abiraterone; rPFS – radiographic progression-free survival; TALA + ENZA – talazoparib with enzalutamide.

Landmark rPFS estimates resulting from each of the FP models are presented in Table 5 alongside predicted rPFS from the company's updated MAIC base case and the Committee's preferred extrapolation of rPFS in NICE TA951. Notably, survival estimates in both the company updated MAIC base case and in TA951 reflect the patient population in the PROpel trial. While these differences are expected because the HRs (either from FP NMA or MAIC) are applied to the TALA + ENZA rPFS and OS based on unadjusted PLD from TALAPRO-2, therefore the model prediction for rPFS and OS for OLAP + AAP is essentially for patients in the TALAPRO-2 study as if they receive OLAP + AAP (which is expected to be different compared with patients in PROpel study receiving OLAP + AAP). Therefore, we do not regard the differences

between modelled rPFS and OS for OLAP + AAP and observed rPFS and OS KM for OLAP + AAP in PROpel study as concerns for the approach.

Figure 8 presents the rPFS extrapolations in the most plausible FP scenario for both TALA + ENZA and OLAP + APP, which also accounted for the capping of rPFS by OS when they cross.

Table 5. rPFS OLAP + AAP survival estimates

Year	TA951 generalised gamma	Updated MAIC base case: log-normal	P = -1 (most plausible FP scenario)	P = -0.5	P = 0
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AAP – abiraterone acetate; rPFS – radiographic progression-free survival.

Figure 8. rPFS in most plausible FP scenario prediction and Kaplan Meier data

Abbreviations: KM, Kaplan Meier; OLA+ABI, Olaparib with abiraterone; rPFS, radiographic progression-free survival; TALA+ENZA, talazoparib with enzalutamide.

OLAP + AAP OS

In addition to poor convergence, the OS FP models generated highly uncertain and implausible HRs over time. OLAP + AAP and TALA + ENZA are assumed to be followed by the same basket of subsequent therapies following disease progression and TALA + ENZA is associated with superior rPFS in all analyses (updated MAIC, FP NMA, PH NMA) therefore it is considered clinically implausible that predicted OS for the OLAP + AAP arm is superior to the TALA + ENZA arm, as is suggested by the predicted HRs over time by some OS FP models. Therefore, time-varying HRs based on FP models for OS were not implemented in the CEM.

Given that the PH assumption appears to hold between TALA + ENZA and OLAP + AAP (see our response to EAG's priority question A4 shared on 24th April 2025) an alternative method for estimating OLAP + AAP OS was used by applying time-constant HR from the MAIC to the unadjusted TALA + ENZA OS extrapolation. In addition to the time-constant HR from the MAIC, alternative time-constant HRs sourced from the fixed-effects and random-effects NMA are available as alternative sources of evidence (in the model settings). The MAIC HR was selected in the most plausible FP scenario as it allows for greater adjustment for prognostic factors observed in the two trials and for consistency with the original and updated MAIC base case.

Table 6. OLAP + AAP vs. TALA+ENZA alternative sources of time-constant OS HR

ITC Approach	Mean HR	95% Credible or CrI lower bound	95% Credible or CrI upper bound
MAIC	[redacted]	[redacted]	[redacted]
NMA: FE	[redacted]	[redacted]	[redacted]
NMA: RE	[redacted]	[redacted]	[redacted]

Abbreviations: FE – fixed effects; HR – hazard ratio; ITC – indirect treatment comparison; MAIC – matching-adjusted indirect comparison; NMA – network meta-analysis; OLAP + AAP – olaparib with abiraterone.

The resulting survival estimates are reported in Table 7 and Figure 9, which reflect OS accounting for general population mortality. Survival estimates from the committee's preferred approach to OLAP + AAP OS from TA951 are presented alongside the

updated MAIC base case and OS time-constant HR approaches as validation of survival estimates.

Table 7. OLAP + AAP survival estimates

Year	TA951 generalized gamma	Updated MAIC base case: generalized gamma	MAIC constant HR	NMA RE constant HR	NMA FE constant HR
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FE – fixed effects; MAIC – matching adjusted indirect comparison; NMA – network meta-analysis; OLAP + AAP – olaparib with abiraterone; RE – random effects.

Figure 9. Most plausible FP scenario (time-constant MAIC HR) OS model prediction and Kaplan Meier data

Abbreviations: KM – Kaplan Meier; OLA+ABI – olaparib with abiraterone; OS – overall survival; TALA+ENZA – talazoparib with enzalutamide.

Table 8 and Table 9 show the undiscounted life-years (Lys) gained between the company's updated MAIC base case and the most plausible FP scenario (rPFS based on FP first-order model with p=-1, OS based on MAIC time-constant HR).

Table 8. Updated MAIC base case - predicted life years (undiscounted)

Technologies	MAIC Updated Base Case			
	rPFS LYs	PD while receiving 2L LYs	PD while receiving Palliative Care LYs	Total LYs
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L – second-line; LY – life-years; MAIC – matching-adjusted indirect comparison; PD – progressed disease; rPFS – radiographic progression-free; TALA+ENZA – talazoparib with enzalutamide.

Table 9. Most plausible FP scenario - predicted life years (undiscounted)

Technologies	Most plausible FP approach			
	rPFS LYs	PD while receiving 2L LYs	PD while receiving Palliative Care LYs	Total LYs
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L – second-line; LY – life-years; MAIC – matching-adjusted indirect comparison; PD – progressed disease; rPFS – radiographic progression-free; TALA+ENZA – talazoparib with enzalutamide.

Incremental LYs using both the company's updated MAIC base case, and the most plausible FP scenario using time-varying rPFS HRs and a time-constant OS HR both indicate a persistent issue with post-progression survival being shorter for TALA + ENZA versus OLAP + AAP which are not deemed clinically plausible by clinical experts. As described in the company addendum submission, both model arms are associated with the same 2L therapies and there is no known clinical mechanism whereby post-progression survival in the OLAP + AAP model arm is expected to be more superior than TALA + ENZA. Therefore, we have also performed an exploratory

surrogate analysis where the OS for TALA + ENZA and OLAP + AAP was estimated by applying a HR of [redacted](95% CrI, [redacted]) to the rPFS for TALA + ENZA and OLAP + AAP, respectively, where the HR was estimated as the HR of OS versus rPFS using PLD in the TALA + ENZA arm in TALAPRO-2. Disaggregated undiscounted LYs resulting from this approach are presented in Table 10 which shows the overall LYs (progressed while receiving second-line treatments and palliative care) are similar between TALA + ENZA versus OLAP + APP ([redacted]).

Table 10: Exploratory surrogate analysis – predicted life years (undiscounted)

Technologies	Explorable surrogate analysis			
	rPFS LYs	PD while receiving 2L LYs	PD while receiving Palliative Care LYs	Total LYs
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]
Incremental	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: 2L – second-line; LY – life-years; MAIC – matching-adjusted indirect comparison; PD – progressed disease; rPFS – radiographic progression-free; TALA+ENZA – talazoparib with enzalutamide.

Most plausible FP scenario results summary

Deterministic results using the most plausible FP scenario are presented in Table 11. One-way sensitivity analysis and probabilistic sensitivity analysis results can be obtained from the submitted CEM.

Table 11. TALA+ENZA vs. OLAP + AAP most plausible FP scenario deterministic results

Technologies	Total			Incremental			ICER per QALY (£)	INMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olaparib with abiraterone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FP, fractional polynomial; ICER – incremental cost-effectiveness ratio; **FP, fractional polynomial;** LYG – life-years gained; mCRPC – metastatic castration-resistant prostate cancer; NMB – net monetary benefit; OLAP + AAP – olaparib with abiraterone acetate; QALYs – quality-adjusted life years; TALA+ENZA – talazoparib with enzalutamide.

The most plausible FP scenario predicts better LY and QALY gains for TALA + ENZA versus OLAP + AAP compared with the updated MAIC base case, meaning the most plausible FP scenario is more favourable to TALA + ENZA regarding incremental effectiveness.

Due to the uncertainty in results from the FP NMA due to the small network and likely short follow-up for the NCT02294461 study, **the company's updated MAIC base case which uses independent parametric models fitted to PROpel KM data and TALA + ENZA MAIC adjusted KM data is still considered to be most appropriate for decision-making.**

B2. Priority: As noted in the email already received from NICE, please include a comparison to enzalutamide within the economic model. As a pragmatic approach it is considered reasonable to do this based upon extrapolation of within trial data.

Pfizer has already informed NICE that the company is willing to accept optimised wording for the potential recommendation in mCRPC, in-line with the following:

"Talazoparib with enzalutamide is recommended, within its marketing authorisation, as an option for untreated hormone-relapsed metastatic prostate cancer in adults who cannot have or do not want chemotherapy. It is only recommended if:

- Olaparib with abiraterone and prednisone or prednisolone would otherwise be offered."

Considering the above, the company does not feel it is necessary to provide a comparison against enzalutamide monotherapy. However, for transparency the company has developed and provided a cost-utility analysis comparing talazoparib with enzalutamide versus enzalutamide monotherapy. The company has supplied this analysis so that they may proceed with discussions around an optimised recommendation against olaparib with abiraterone.

Economic base case

rPFS, OS and TTD data used to inform the cost-utility analysis were derived from the final data cut of TALAPRO-2 (data cutoff: 3rd September 2024). Deterministic base case results from the newly developed economic model are presented in Table 1. A PAS discount of [redacted] is applied to talazoparib in the economic model.

Table 1. Deterministic base case results

Technologies	Total			Incremental			ICER per QALY (£)	NMB at £30,000
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
Talazoparib with enzalutamide	[redacted]	[redacted]	[redacted]	-	-	-	-	-
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; NMB – Net monetary benefit; QALYs – Quality-adjusted life years

Radiographic progression free survival

Unlike the cost-utility analysis between talazoparib with enzalutamide versus olaparib with enzalutamide, the cost-utility analysis presented here utilises Kaplan-Meier (KM) data for rPFS and OS directly from TALAPRO-2 rather than weighted KM data from a MAIC. Considering these data are different, it was necessary to re-select parametric distributions for both rPFS and OS extrapolation.

The company adopted a log-normal distribution for rPFS and OS in both arms in the base case. For rPFS, the log-normal distribution provided the best statistical fit, with the lowest sum AIC/BIC. Landmark estimates for the log-normal distribution compared to KM data were relatively consistent across the examined timepoints, with moderate variation observed at 48 months (Table 2 & 3).

The overlay of the parametric curve on the KM plot demonstrated good visual fit, with no kinks observed in the plot, further supporting the adoption of the log-normal distribution for rPFS (Figure 1). The overlay of the KM plots with all the examined parametric curves is presented in Figure 2 & 3.

Table 2. Goodness-of-fit statistics and survival predictions for talazoparib with enzalutamide rPFS parametric distributions in the enzalutamide economic model

Distribution	Goodness-of-fit				rPFS							
	AIC*	BIC*	Sum of AIC and BIC*	Sum rank*	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data												
Log-normal												
Generalized gamma												
Log-logistic												
Weibull												
Gompertz												
Exponential												
Gamma												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier; rPFS – Radiographic progression-free survival
*Data relate to both arms (talazoparib with enzalutamide as well as enzalutamide)

Table 3. Goodness-of-fit statistics and survival predictions for enzalutamide rPFS parametric distributions in the enzalutamide economic model

Distribution	Goodness-of-fit				rPFS							
	AIC*	BIC*	Sum of AIC and BIC*	Sum rank*	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data												
Log-normal												
Generalized gamma												
Log-logistic												
Weibull												
Gompertz												
Exponential												
Gamma												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier; rPFS – Radiographic progression-free survival
*Data relate to both arms (talazoparib with enzalutamide as well as enzalutamide)

Figure 1. rPFS log-normal for both treatment arms

Abbreviations: ENZA – enzalutamide; rPFS - radiographic progression-free survival; TALA – talazoparib; TP-2 – TALAPRO-2

Figure 2. Talazoparib with enzalutamide KM for rPFS overlaid with the extrapolated parametric survival curves

Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; rPFS – Radiographic progression-free survival; TALA – Talazoparib; TP-2 – TALAPRO-2

Figure 3. Enzalutamide KM for rPFS overlaid with the extrapolated parametric survival curves

Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; rPFS – Radiographic progression-free survival; TP-2 – TALAPRO-2

Overall survival

For OS, upon examining the parametric curves, only the log-normal and exponential distributions did not exhibit kinks. Therefore, only the log-normal and exponential distributions were considered for OS. The log-normal distribution is a better statistical fit compared to the exponential distribution, with a lower sum AIC/BIC. Landmark estimates for the log-normal distribution compared to KM data were relatively consistent across the examined timepoints, with moderate variation observed at 24 months for both arms and at 48 months for the enzalutamide arm. The log-normal distribution also better aligned to the KM landmark estimates compared to the exponential distribution (Table 4 & 5). Additionally, both the log-normal and exponential distributions align reasonably well with clinical advice to the EAG in TA951, suggesting "OS of 8 – 10% at 10 years is expected using current care options".[1] The log-normal distribution also provided a better visual fit in the overlay of the parametric curves on the KM plot compared to the exponential distribution, further supporting the adoption of the log-normal distribution for OS (Figure 4 & 5).

The overlay of the KM plots with all the examined parametric curves is presented in Figure 6 & 7.

Table 4. Goodness-of-fit statistics and survival predictions for talazoparib with enzalutamide OS parametric distributions in the enzalutamide economic model

Distribution	Goodness-of-fit				OS							
	AIC*	BIC*	Sum of AIC and BIC*	Sum rank*	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data	[redacted]											
Log-logistic												
Gamma												
Generalized gamma												
Weibull												
Log-normal												
Gompertz												
Exponential												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier; OS – Overall survival
*Data relate to both arms (talazoparib with enzalutamide as well as enzalutamide)

Table 5. Goodness-of-fit statistics and survival predictions for enzalutamide OS parametric distributions in the enzalutamide economic model

Distribution	Goodness-of-fit				OS							
	AIC*	BIC*	Sum of AIC and BIC*	Sum rank*	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data	[redacted]											
Log-logistic												
Gamma												
Generalized gamma												
Weibull												
Log-normal												
Gompertz												
Exponential												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; KM – Kaplan-Meier; OS – Overall survival
*Data relate to both arms (talazoparib with enzalutamide as well as enzalutamide)

Figure 4. OS log-normal for both treatment arms

Abbreviations: ENZA – enzalutamide; rPFS - radiographic progression-free survival; TALA – talazoparib; TP-2 – TALAPRO-2

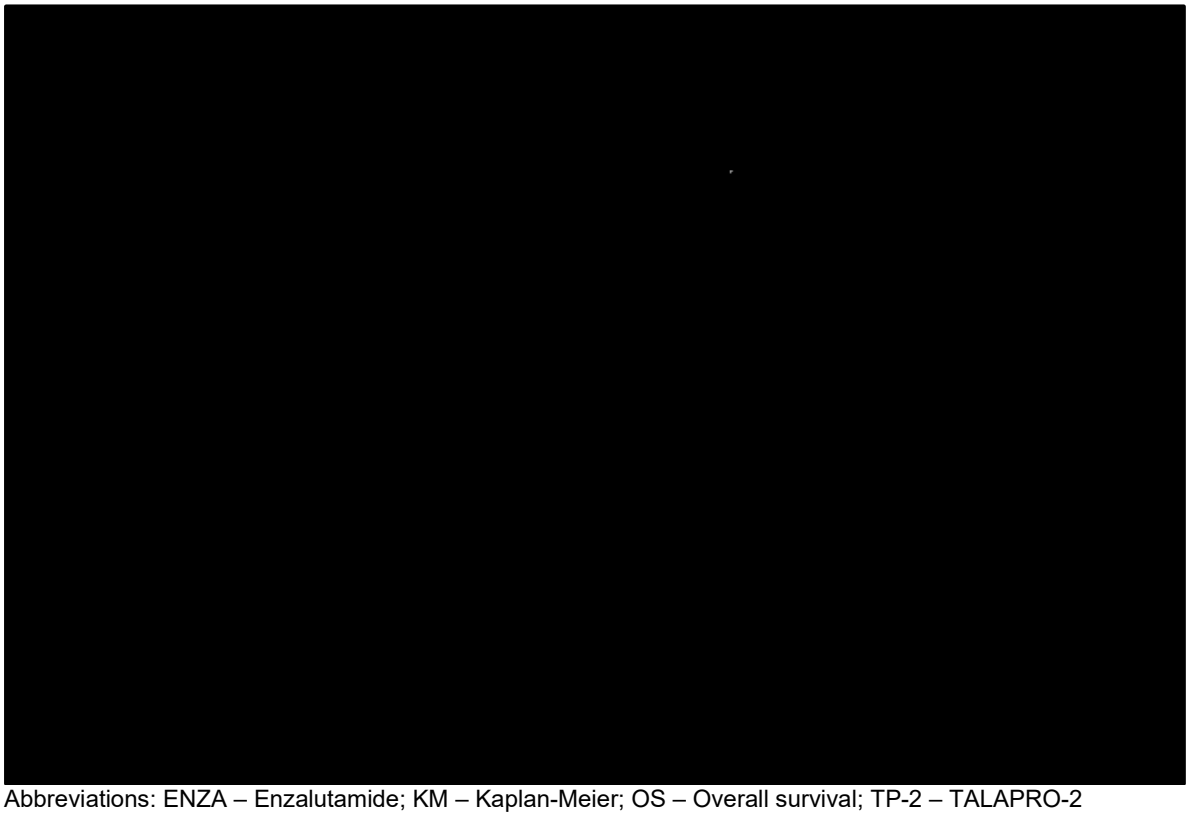
Figure 5. OS exponential for both treatment arms

Abbreviations: ENZA – enzalutamide; rPFS - radiographic progression-free survival; TALA – talazoparib; TP-2 – TALAPRO-2

Figure 6. Talazoparib with enzalutamide KM for OS overlaid with the extrapolated parametric survival curves

Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; OS – Overall survival; TALA – Talazoparib; TP-2 – TALAPRO-2

Figure 7. Enzalutamide KM for OS overlaid with the extrapolated parametric survival curves



Abbreviations: ENZA – Enzalutamide; KM – Kaplan-Meier; OS – Overall survival; TP-2 – TALAPRO-2

Time to treatment discontinuation

For TTD, the log-logistic distribution provided the best statistical fit, with lowest sum AIC/BIC for the respective arms. Landmark estimates for the log-logistic distribution matched KM data well across the examined timepoints (Table 6-8). Therefore, the log-logistic distribution was selected to model TTD. This selection is in-line with the new base case of the cost-utility model against olaparib with abiraterone, as the same KM data was used for the talazoparib with enzalutamide arm.

Table 6. Goodness-of-fit statistics and survival predictions for talazoparib in talazoparib with enzalutamide arm TTD parametric distributions

Distribution	Goodness-of-fit				TTD							
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data												
Log-logistic												
Log-normal												
Generalized gamma												
Exponential												
Gompertz												
Weibull												
Gamma												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; TTD – Time-to-treatment discontinuation

Table 7. Goodness-of-fit statistics and survival predictions for enzalutamide in talazoparib with enzalutamide arm TTD parametric distributions

Distribution	Goodness-of-fit				TTD							
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data												
Log-logistic												
Generalized gamma												
Log-normal												
Gompertz												
Exponential												
Gamma												
Weibull												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; TTD – Time-to-treatment discontinuation

Table 8. Goodness-of-fit statistics and survival predictions for enzalutamide in the enzalutamide arm TTD parametric distributions

Distribution	Goodness-of-fit				TTD							
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
KM data												
Log-logistic												
Generalized gamma												
Log-normal												
Gompertz												
Exponential												
Gamma												
Weibull												

Abbreviations: AIC – Akaike information criterion; BIC – Bayesian information criterion; TTD – Time-to-treatment discontinuation

Scenario analysis

In the new base case of the cost-utility analysis versus olaparib with abiraterone log-normal was used for rPFS and generalised gamma was used for OS extrapolation. When adopting similar parametric distributions for rPFS and OS, kinks in both the talazoparib with enzalutamide and the enzalutamide monotherapy rPFS curves arise at ~7 years and ~10 years, respectively. Considering the high likelihood of the rPFS and OS KMs crossing before these timepoints (i.e. patients likely dying from non-progression related events due to high background mortality at old age), kinks in the rPFS curve may reflect real UK clinical practice. Therefore, the company acknowledges it may not be appropriate to discredit scenarios with kinks in the rPFS curve as a potentially viable base case. That said, a scenario which utilises log-normal for rPFS and generalised gamma for OS extrapolation (similar to new base case in cost-utility analysis versus olaparib with abiraterone) is presented in Table 9. Another scenario which utilises log-normal for rPFS and log-logistic for OS extrapolation is also presented in Table 9. This scenario utilises the best statistical fits with the lowest sum AIC/BIC for rPFS and OS, respectively.

Enzalutamide will be losing patent protection (loss of exclusivity [LOE]) in June 2028 in the UK. After LOE, under the most recent Voluntary Scheme for Branded Medicines Pricing and Access (VPAG) criteria, it will be classified as an 'older medicine' and required to pay a rebate which guarantees the NHS a minimum 35% reduction from list price (whether delivered through price cuts or VPAG rebates).[2] A scenario accounting for reduction of list price based on the current VPAG rebate rates is presented in a Table 9.

More realistically, the entry of generic competition into the market will have a much greater impact on the price paid by the NHS for enzalutamide. Our recent experience of tendering for other oral oncology medicines, and information provided by NHSE through tender award debriefs suggest at least a [redacted] reduction in list price can be expected. A scenario considering the impact of enzalutamide's loss of exclusivity is presented in Table 9. Of note, once enzalutamide losses exclusivity in the UK, talazoparib with enzalutamide becomes a cost-effective treatment option to the NHS in the economic model base case at a £30,000 per QALY threshold.

Table 9. Scenario analysis results

Scenario analysis	Incremental costs (£)	Incremental QALYs	ICER per QALY (£)	% change
Base case	[redacted]	[redacted]	[redacted]	-
Log-normal rPFS and generalised gamma OS (as per new base in CUA versus olaparib with abiraterone)	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal rPFS and log-logistic (lowest sum AIC/BIC)	[redacted]	[redacted]	[redacted]	[redacted]
VPAG LOE discount (35% discount on list price)	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide LOE (90% discount on list price)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC – Akaike's information criterion; BIC – Bayesian information criterion; CUA – cost-utility analysis; ICER – incremental cost-effectiveness ratio; LOE – loss of exclusivity; QALY – quality-adjusted life year; VPAG – Voluntary Scheme for Branded Medicines Pricing and Access

Follow-up questions from EAG (received 2nd May 2025)

1. Please could you supply tables (in the format used for the response to clarification question B3) behind the curve fitting for talazoparib and enzalutamide for TTD (this wasn't included in the clarification response)

Tables summarising goodness-of-fit for talazoparib and enzalutamide TTD have now been added to B2 above (Table 6-8). Since TTD data for talazoparib and enzalutamide are consistent between the olaparib with abiraterone model and the enzalutamide model, these data apply to both.

2. The EAG spotted a difference between the rPFS and OS mean AUC supplied in the tables and the model. On investigation, they think this is because the company (in error) have selected unstratified rather than stratified curves. Please could the company confirm this and fix it when they send the model with enzalutamide monotherapy included.

The company confirm that the rPFS and OS AUC values provided in question B3 are correct. These values reflect the unstratified curve distributions, pre-transformation. The transformations applied in the model are as follows:

- rPFS: Check for crossing with OS, and if so, use the OS value
- OS: Check for crossing with general population mortality, and if so, use the general population mortality value
- TTD: Check for crossing with rPFS, and if so, use the rPFS value

The company provided the pre-transformed values as these are more suitable to reflect the true values associated with the distributions, in isolation of the other curve selections. Transformed curves are subject to the distribution selection for the other outcomes.

The pre-transformed curve values are displayed alongside the transformed values in the ‘rPFS calcs’, ‘OS calcs’, and ‘TTD calcs’ sheets of the economic model.

The company supplied the seven unstratified standard parametric curve distributions (exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, and Weibull) in line with TA951[1] and the recommendation of NICE DSU TSD14[3].

References

1. NICE. TA951. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. https://www.nice.org.uk/guidance/ta951/resources/olaparib-with-abiraterone-for-untreated-hormonerelapsed-metastatic-prostate-cancer-pdf-82615723963333
2. ABPI. How company payments are calculated under the 2024 VPAG. https://www.abpi.org.uk/value-and-access/uk-medicine-pricing/voluntary-scheme-on-branded-medicines/how-company-payments-are-calculated-under-the-2024-vpag/
3. Latimer NR. Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data: Inconsistencies, Limitations, and a Practical Guide. Medical Decision Making. 2013/08/01 2013;33(6):743-754. doi:10.1177/0272989X12472398

Validation

B17. Please provide a comparison of the outputs of the economic analysis presented to previous technology appraisals.

Pfizer would like to thank NICE for sourcing confidential landmark rPFS and OS estimates from TA951[1], as well as progressed disease health state utility values used in TA887[2] and TA951[1]. Based on this information, we have been able to validate rPFS and OS curve selection in the talazoparib with enzalutamide versus olaparib with abiraterone (OLA+ABI) economic model. Unredacted data from TA951[1] have also been considered in the fractional polynomial (FP) network meta-analysis (NMA) carried out in response to clarification question A6 (please refer to ID4004_Prostate talazoparib clarification question A6_FP NMA_28MAY25_[CON]). Scenarios utilising the progressed disease health state utility values from TA887[2] and TA951[1] are also presented for transparency for both the OLA+ABI model and the talazoparib with enzalutamide versus enzalutamide monotherapy (ENZA) model, demonstrating the impact on the base case ICER.

rPFS curve selection – OLA+ABI model

Table 1 compares landmark estimates for rPFS from each of the parametric distributions fitted to the OLA+ABI arm (adjusted OLA+ABI KM from the MAIC) in the OLA+ABI model against the TA951[1] base case (generalised gamma). When using the log-normal distribution to model rPFS for OLA+ABI (as in the updated base case) or the generalised gamma (old base case) the rPFS estimates are similar to those in TA951[1] for months 12 and 24 where values differ by [redacted]. At months 48, the rPFS estimates differ slightly when using the log-normal ([redacted]) compared the generalised gamma ([redacted]) estimate which is closer aligned to the TA951[1] base case ([redacted]). At Month 120, the log-normal and generalised gamma curve deviate further ([redacted] vs [redacted], respectively), with the generalised gamma again closer aligned to the TA951[1] base case ([redacted]).

Despite the closer alignment of the generalised gamma distribution to TA951[1] at months 48 and 120, the company believe that the log-normal distribution represents a more suitable base case selection. Though the rPFS values provided below are closer aligned to TA951[1], when the generalised gamma distribution is selected in the model, these values are overwritten by the lower OS values, creating a kink in the rPFS curve, whereas the log-normal curve does not incur a kink. The log-normal distribution also provides a better statistical fit, a good visual fit, and the landmark estimates, although different to generalised-gamma at months 48 and 120, are reasonable.

Table 1. Goodness-of-fit statistics and survival predictions for olaparib with abiraterone rPFS parametric distributions

Distribution	Goodness-of-fit				rPFS					
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	48 months (%)	120 months (%)
TA951 base case (gen gamma)										
KM data										
Log-normal										
Generalised gamma										
Log-logistic										
Gamma										
Weibull										
Exponential										
Gompertz										

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; NA – Not available; rPFS – Radiographic progression-free survival

OS curve selection – OLA+ABI model

Table 2 compares the landmark estimates for OS from each of the parametric distributions fitted to the OLA+ABI arm (adjusted OLA+ABI KM from the MAIC) in the OLA+ABI model against the TA951[1] base case. The landmark OS estimates for the generalised gamma distribution, match very closely with those from TA951[1] for all reported months (months 12, 24, 48 and 120). The generalised gamma distribution also has a good statistical and visual fit. Therefore, the company believes the selection of the generalised gamma distribution for modelling OS in the OLA+ABI arm of the model base case is justified.

Table 2. Goodness-of-fit statistics and survival predictions for olaparib with abiraterone OS parametric distributions

Distribution	Goodness-of-fit					OS						
	AIC	BIC	Sum of AIC and BIC	Sum rank	Mean area under curve (months)	Median (months)	12 months (%)	24 months (%)	36 months (%)	48 months (%)	60 months (%)	120 months (%)
TA951 base case (gen gamma)	-	-	-	-	-							
KM data										-	-	-
Log-normal												
Generalised gamma												
Log-logistic												
Gamma												
Weibull												
Exponential												
Gompertz												

Abbreviations: AIC – Akaike Information Criteria; BIC – Bayesian Information Criteria; NR – Not reached; OS – Overall survival

Progressed disease health state utilities – OLA+ABI model and ENA model

The progressed disease state (PDa) utility value used in TA951[1] was [redacted], while TA377[3] used 0.658, and TA887[2] used [redacted].

For both the OLA+ABI model and the ENZA model (ENZA model submitted in response to question B2), the company applied a progressed disease health utility value of 0.658 in the base case, based on the post-progression health state utility value used in TA377[3]. The company considers this to be the most robust utility value, as it is [redacted], providing a fair and reflective representation of the health state in the landscape. As such, the 0.658 value from TA377[3] has been kept in the company base case.

However, for transparency, we have provided scenario analyses utilising the progressed disease health state utility values from TA887[2] and TA951[1] to demonstrate the impact on the base case ICER in the OLA+ABI model (Table 3) and the ENZA model (Table 4), respectively. Overall, varying the progressed disease health state utility had minimal impact on the base case ICERs in both economic models.

In the OLA+ABI model (Table 3), utilising the progressed disease health state utility value from TA951[1] incurred a minor decrease in incremental QALYs. Conversely, utilising the progressed disease health state utility value from TA887[2] resulted in a minor increase in incremental QALYs. The ICER remained dominating despite the selection of progressed disease health state utility value.

Table 3. Impact of using alternative progressed disease utilities – OLA+ABI model

	Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)
Base case (TA377 progressed disease utility value)	[redacted]	[redacted]	[redacted]
Scenario: TA951[1] progressed disease utility value	[redacted]	[redacted]	[redacted]
Scenario: TA887[2] progressed disease utility value	[redacted]	[redacted]	[redacted]

Abbreviations: ABI – abiraterone; ICER – incremental cost-effectiveness ratio; OLA – olaparib; QALY – quality-adjusted life year.

In the ENZA model (Table 4), utilising the progressed disease health state utility value from TA951[1] incurred a minor decrease to the incremental QALYs and in turn a minor increase to the base case ICER ([redacted]). Conversely, utilising the progressed disease

health state utility value from TA887[2] resulted in a minor increase in incremental QALYs and in turn a minor decrease to the base case ICER ([redacted]).

Table 4. Impact of using alternative progressed disease utilities – ENZA model

	Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)
Base case (TA377 progressed disease utility value)	[redacted]	[redacted]	[redacted]
Scenario: TA951[1] progressed disease utility value	[redacted]	[redacted]	[redacted]
Scenario: TA887[2] progressed disease utility value	[redacted]	[redacted]	[redacted]

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

Additional EAG queries on stratification of curves – received 20th May 2025

Please can you clarify whether in the economic model you had intended to select unstratified curves? Please provide a justification for this.

- The EAG notes that the original submission states stratified curves were intended to be used in the economic model (page 34: "independent models were fitted to each arm in the model") and according to the EAG the statistics sent in response to clarification B3 / B4 appear to be from stratified curves (AIC / BIC values differ per arm) whereas the statistics sent for the enzalutamide comparison are from unstratified curves.

We would like to point out that this interpretation of the AIC/BIC values is incorrect; the OLA+ABI values in the statistics in response to clarification questions B3/B4 relate to unstratified curves (as well as those provided for the ENZA model).

The statement on page 34 ("independent models were fitted to each arm in the model") alludes not to the direct stratification of the parametric curves, but to the ability to select curves for outcomes and comparators separately, as opposed to utilising a hazard ratio. Since independent models are fitted for each arm in the model in both the OLA+ABI and ENZA models, the curves could be termed 'stratified' in the sense that multiple arms are not pooled in the calculations. In methodological terms, however, an 'unstratified curve' approach was applied for both models since as the inputs were treated as one group.

The seven parametric curve options presented in the model are aligned with TA951[1] and the recommendation of NICE DSU TSD14[4]. Further information is provided in our response to EAG follow up clarification questions No. 2, shared with our response to clarification question B2 on 15th May 2025.

For the unstratified analysis, please can you provide the MAIC-weighted olaparib with abiraterone Kaplan Meier data in Excel format to allow visual comparison of the curve fits included in the current company base case.

- The EAG have assumed that the current graphics provided use the stratified curves

As the curves presented in the model are unstratified, the AIC/BIC values provided in response to clarification question B3 also relate to unstratified curves. For the OLA+ABI model, MAIC AIC/BIC values have been provided relevant to each arm; this does not mean that the selected parametric curves are stratified, it only implies that the user can select different parametric curves for the TALA+ENZA arm and the OLA+ABI arm. In the ENZA model, where the comparator selection/setting (ENZA) is associated with both arms, it is suitable to present the AIC/BIC values together for both arms.

References

1. NICE. TA951. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. https://www.nice.org.uk/guidance/ta951/resources/olaparib-with-abiraterone-for-untreated-hormonerelapsed-metastatic-prostate-cancer-pdf-82615723963333
2. NICE. TA887. Olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer. https://www.nice.org.uk/guidance/ta887/chapter/3-Committee-discussion
3. NICE. TA377. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. https://www.nice.org.uk/guidance/ta580/documents/committee-papers
4. Latimer NR. Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data: Inconsistencies, Limitations, and a Practical Guide. *Medical Decision Making*. 2013/08/01 2013;33(6):743-754. doi:10.1177/0272989X12472398

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

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

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- Your response should not be longer than 10 pages.

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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 the UK's leading charity for men with prostate cancer and prostate problems. We support men and provide information, find answers through funding research and lead change to raise awareness and improve care. The charity is committed to ensuring the voice of people affected by prostate disease is at the heart of all we do.
4b. Has the organisation received any funding from the 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.**	Amounts received below are from the time period between 2022 and 2024: Astellas Pharma – £33,500 – Prostate Cancer UK Improvement Programmes AstraZeneca - £10,350 - Prostate Cancer UK Improvement Programmes Pfizer - £450 – unrestricted Janssen - £60,000 – PSA Consensus
4c. Do you have any direct or indirect links	no

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Literature searches using trusted databases such as PubMed and knowledge based on communications with patient stakeholders. We have spoken directly with men in this indication and with our specialist nurses about their experience of speaking with men in this indication.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Men with advanced disease can present with a number of different symptoms. Evidenced symptoms for advanced prostate cancer can include: • Fatigue. • Pain, most commonly caused by prostate cancer that has spread to the bones. • Urinary problems, this includes problems emptying the bladder, incontinence, blood in urine and kidney problems. • Bowel problems including constipation, diarrhoea, faecal urgency, faecal incontinence, pain, bowel obstruction and flatulence. • Broken bones, fractures caused by bone thinning. • Sexual problems, including reduced libido and difficultly getting or keeping an erection. • Lymphoedema, primarily around the legs. • Anaemia, caused by damage to bone marrow. • Metastatic spinal cord compression, as cancer cells grow in or near the spine, which evidence suggests can occur in 1 to 12% of patients[i]. • Hypercalcaemia, caused by calcium leaking from the bones into the blood. • Eating problems Men with hormone resistant metastatic prostate cancer (mCRPC) have a limited number of treatments available to them. At this stage of the disease, men may experience more significant symptoms due to the disease becoming more aggressive when hormone resistance occurs. Different symptoms from their prostate cancer (depending on where their cancer is) can include: • Pain may develop which for some men with mCRPC can be significant. • Men with advanced prostate cancer who have bone metastasis, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem.

	• Bone metastasis can also result in spontaneous fractures, without trauma and increased risk of fracture associated with trauma. • For men whose prostate cancer affects their bone marrow, they may become anaemic (therefore becoming more tired or becoming breathless) requiring blood transfusions, thrombocytopenia (prone to bruising and bleeding), and develop low white blood cell counts (making them more susceptible to infection). • Visceral metastases can involve the liver and the lungs, causing considerable morbidity; brain metastases commonly result in significant and distressing neurological deficits. • Weight loss and reduced appetite can often be a particular concern for carers. • If prostate cancer advances in the region around the prostate, men may experience urinary tract problems and renal problems. It is important to note that men are unlikely to experience all the above symptoms, as some will depend on the treatments received, while others will be the result of metastases and therefore dependent on their location. The severity of symptoms will also differ among men. For some men, living with metastatic prostate cancer can be hard to deal with emotionally, especially as there are no current curative treatments for this stage of the disease. Symptoms and treatments can be draining and make men feel unwell. And some treatments, including hormone therapy, can make men feel more emotional and cause low moods. The pressure of advanced cancer can also put a strain on relationships. Metastatic prostate cancer and its treatments might mean that partners or family need to do more for patients, such as running the home or increasing caring responsibilities. Additionally, the symptoms described for mCRPC and the side effects of treatments can make it difficult to work. A partner providing care might not be able to work as much either. Everyday tasks may become more difficult and respite care may be required to give carers a break. As the disease progresses, more palliative care and treatments will be offered. This includes palliative radiotherapy to ease bone pain, blood in urine and swollen lymph nodes.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Inevitably, men and their families express disappointment and even fear that there are no curative treatments for metastatic hormone-resistant prostate cancer. Many are interested in clinical trials with the hope of improving their life expectancy. In the hormone-resistant setting men can receive docetaxel, abiraterone, enzalutamide, or cabazitaxel (if they have already had a previous round of docetaxel). Radium 223 is a further last line treatment. There is also olaparib available for a small group of men who have been previously treated with an NHA and have a BRCA1 or 2 mutation. The combined treatment of olaparib with abiraterone is available for metastatic hormone resistant men who are untreated. Docetaxel chemotherapy is only offered to those felt fit enough to receive it. It will be offered in the hormone-sensitive stage initially, but there is an opportunity for rechallenge or new administration in the castrate-resistant setting. While there are side-effects from chemotherapy, severe side effects are reported mostly during treatment and in the first 6 months after treatment. Adverse events include fatigue, alopecia, nausea/vomiting, diarrhoea, nail changes and sensory neuropathy[ii] . Many men and their families are fearful of chemotherapy. Most men develop low blood counts making them vulnerable to infection, some of which are potentially life-threatening infections. Many men say that the taste changes that the chemotherapy can cause is extremely difficult to live with, adversely affecting their quality of life. Treatment means going into hospital, often to clinic on one day followed by chemotherapy the next day approximately every three weeks for 6 cycles of treatment. Some men travel long distances to receive their treatment. They are also required to self-monitor between visits, to be vigilant, recognise and to present back to hospital should any adverse reactions to treatment occur, for example, should they become febrile. Many men find this onerous and extremely anxiety provoking. This treatment regimen and side effect profile are similar to that of cabazitaxel as well. Abiraterone and enzalutamide have different side-effect profiles. Adverse events for abiraterone include fatigue, back pain, nausea, constipation, bone pain, arthralgia and oedema. Abiraterone is also associated with an elevation in aminotransferase levels which can lead to more frequent monitoring with liver-function tests during treatmentiii. Adverse events for enzalutamide include fatigue, back pain, constipation and arthralgia[iv].

8. Is there an unmet need for patients with this condition?	Patient organisations, and the patients themselves, believe there is a strong need for further treatments that offer good clinical benefit and improvement in the median overall survival, as this remains low past 18 months - docetaxel offers a median survival benefit of less than 3 months if given first in the castrate-resistant stage[v], abiraterone and enzalutamide, without a direct comparison, offer similar survival benefit, 3 months for abiraterone[vi] and 5 months for enzalutamide[vii]. Radium 223 offers a median of just under 3 months of additional life[viii]. There are numerous treatments available for prostate cancer in the metastatic castrate-resistant setting. However, there is uncertainty in how each patient will respond or tolerate any treatment and so more treatments need to be made available to make sure every patient can have the best treatment that suits them and their cancer best. This is especially pertinent as these patients cannot be cured, so extension of good quality life is imperative to these patients.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Men with prostate cancer want more treatments to be available to them, that work for them. This treatment combination offers patients not only another treatment choice at this point in the pathway, but more certainty around surviving for longer. In the TALAPRO-2 trial, the median progression-free survival (judged on imaging), was 37% better in the talazoparib plus enzalutamide arm vs the placebo plus enzalutamide arm, and median rPFS was not reached in this arm. The trial also demonstrated that talazoparib in combination with enzalutamide led to a 54% reduction in the risk of progression or death compared to the placebo in combination with enzalutamide as a first-line treatment for the combined HRR-deficient population. These findings further support the previous analysis of patients (PROpel) with HRR-deficient tumours in the overall study population and thus highlights the therapeutic potential of this treatment combination for men in this indication, particularly in the HRR deficient subgroup. We also know, from speaking with patients and carers about treatment options, that ease of administration is a key factor in choosing a treatment. Treatment with enzalutamide and talazoparib provides an option for patients to administer their treatment in the comfort of their own home as it is in oral form. This is in comparison to the administration of chemotherapy where a patient will need to travel into hospital multiple times over a few months and spend considerable time there for its administration. Patients who are considered to be in this indication, especially those in this indication who are also contra-indicated to docetaxel, and also abiraterone, prednisolone, or olaparib and thus would not be eligible to have these as alternative treatment options, could benefit from talazoparib with enzalutamide and it's subsequent increase in progression free survival.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Unfortunately this treatment combination may not be the correct choice of treatment for some patients who may have other medical issues which could be exacerbated by the medication, or are more frail due to its side effect profile. This includes anaemia and those who may be immunocompromised. This treatment could also affect those with bleeding disorders.

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 stated in section 9, this treatment could be of benefit for those patients who are unable to tolerate the effects of chemotherapy or the effects of the combined treatment of abiraterone and olaparib.

Equality

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

Other issues

13. Are there any other issues that you would like the committee to consider?	n/a

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Men in this indication need more treatment choice • Patients who cannot tolerate chemotherapy or who do not want chemotherapy would benefit most from this treatment • Talazoparib in combination with enzalutamide led to a 55% reduction in the risk of progression or death compared to the placebo in combination with enzalutamide as a first-line treatment for the combined HRR-deficient population. •

Thank you for your time.

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[i] European Urology Volume 44 Issue 5 *Spinal Cord Compression in Metastatic Prostate Cancer* H Tazi et al. November 2003
[ii] New England Journal of Medicine *Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer*. Tannock et al. October 2004
[iii] https://www.nejm.org/doi/full/10.1056/NEJMoa1014618
[iv] https://www.nejm.org/doi/full/10.1056/NEJMoa1405095
[v] https://www.nejm.org/doi/full/10.1056/NEJMoa041318
[vi] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3471149/
[vii] https://www.nejm.org/doi/full/10.1056/NEJMoa1207506
[viii] https://www.nejm.org/doi/full/10.1056/NEJMoa1213755

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

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

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- 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 also support local prostate cancer support groups around the UK. We represent nearly 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 are funded from many sources: Gifts from the public, Trust income, Lottery grant, income from the pharma industry for specific projects or as unrestricted grants
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	Accord £5,000 (Unrestricted grant) Astellas £9,600 (Project based grant)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
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 online as well as in person. Additionally, we engage in direct communication with individuals and address questions and concerns raised by patients through local patient helplines and via our national website. Our medical advisory board is in place to offer guidance whenever necessary.

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?	The transition from having a cancer that is hormone sensitive to one that is hormone resistant (castrate resistant) is one that will involve considerable changes in that patient – both physiologically and psychologically. For many it is a debilitating and life-changing problem. It may occur after a period of hormone therapy lasting very many years or which can be barely a year or even months depending on the aggressiveness of the cancer itself. Hormone therapy may have been the sole treatment or given in addition to other potential radical therapies such as surgery or radiotherapy. Many patients with advanced prostate cancer will progress to experience multiple problems such as bone pain, spinal cord compression, anaemia, fatigue. The psychological impact of knowing there is now a limited lifespan and a very uncertain future can produce significant psychological traumas in both the patient and those who care for him. Relationships will come under strain and may alter. As the disease progresses, increased amounts of care may be needed by the patient. There will almost invariably be a progressive reduction in quality of life.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Both the patient and those looking after him will be devastated that the current treatment regime has failed and that curative treatment is no longer a reality. Some will express considerable distress and indeed anger at the perceived failure of that treatment. They standard practise in this situation would be to add a further therapeutic agent to the hormone therapy which is failing. Treatments that can be added are one of the novel hormonal agents (NHAs) (abiraterone, enzalutamide, apalutamide, darolutamide) or chemotherapy with docetaxel. For patients with metastatic disease at the time of initial diagnosis, standard of care is now to start hormone therapy and to offer chemotherapy or novel hormonal agents at that time. Unfortunately, it would appear that a significant number of patients are still only offered hormone therapy as a sole agent. Obviously patients will wish for additional treatment that is effective, with an acceptable level of side effects to produce both an increase in *quantity* of life as well as *quality* of life. Whilst chemotherapy is effective for some patients, some may be unsuitable for such treatment. Current therapy is mainly based on what can be best described as *'serial monotherapy'* where a single drug is used to control symptoms until that treatment fails and another one is used. However in many other cancers combinations of drug therapies, each of which has a different mode of action, are used i.e. *'rational polytherapy'.* Until recently this has not been the case with the treatment of mHRPC. NICE have recently approved the combination of Olaparib and Abiraterone to be used here. (NICE technology appraisal guidance 951). Olaparib is a PARP inhibitor working along homologous recombination repair (HRR) pathways and Abiraterone an established NHA.
8. Is there an unmet need for patients with this condition?	Yes. Some patients will not be clinically suitable got the already established regime of Olaparib / Abiraterone, This different combination will allow those patients to still benefit for the combination technology of a PARP inhibitor and NHA.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients, carers and indeed patient support groups strive to ensure that PCa patients get the most effective treatments available, and that these treatments are available to all appropriate patients. Response to treatments can be variable between patients and thus a wide range of treatments for clinicians to choose from is highly desirable. The combination of a PARP inhibitor and NHA (Olaparib and Abiraterone has already been appraised and cost approved by NICE. Because this current appraisal is just a cost comparison exercise, it is assumed that the combination under review has a similar efficacy. Therefore it would seem logical that if costs of the Talazoparib and Enzalutamide combination are similar (or even less) then this combination should also be approved. This different drug combination would allow patients who are clinically unsuitable for Abiraterone as the NHA component to have a similar treatment using Enzalutamide. The main advantage is simple: extension of life with a reasonable quality of life for as long as possible. The option of oral treatments is superior for most patients than chemotherapy requiring visits to a hospital. That there is now choice of NHA for those who may be unsuitable for Abiraterone in combination with a PARP inhibitor is also a great advantage.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The incidence of side effects will always be a disadvantage, but trials indicate that the extra burden of Talazoparib did not add unacceptable degrees of side effects for most patients. Those patients who are already frail and have a low ECOG status may not be suitable for this therapy but will almost certainly be unsuitable for many other potent treatments for mHRPC as well.

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 stated above, some patients may have co-morbidities which make them clinically unsuitable for the individual drugs in question. However, those unsuitable for one NHA may be suitable for the other. The ability of choice is a great advantage

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	As with any newly introduced medication, whether patients are prescribed that medication depends on many factors such as clinician experience, local prescribing guidelines, local funding arrangements etc. The phenomenon of a 'postcode lottery' can be a factor.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• The transition from having a cancer that is hormone sensitive to one that is hormone resistant (castrate resistant) is one that will involve considerable changes in that patient – both physiologically and psychologically. Both the patient and those looking after him will be devastated that the current treatment regime has failed, and that curative treatment is no longer a reality. • It is becoming established that the treatment of advanced prostate cancer may be better achieved by using a combination of drugs at the same time rather than using those drugs in a serial fashion. • One such combination (Olaparib with Abiraterone) has already been costed and approved by NICE. • The combination under review can be similarly effective in clinical practice. This review is a cost comparison exercise. It does not directly compare the two regimes clinically. • The combination therapy of Talazoparib and Enzalutamide can be used in those patients clinically unsuitable for the currently approved combination. This fills a hitherto unmet need.

Thank you for your time.

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Single Technology Appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

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.

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

Please underline all confidential information, and separately highlight information that is submitted 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 30 June.** 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.

Part 1: Treating untreated hormone-relapsed metastatic prostate cancer and current treatment options

Table 1 About you, aim of treatment, place and use of talazoparib with enzalutamide, sources of evidence and equality

1. Your name	Suneil Jain
2. Name of organisation	Queen's University Belfast
3. Job title or position	Prof of clinical oncology
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 untreated hormone-relapsed metastatic prostate cancer? ☒ A specialist in the clinical evidence base for untreated hormone-relapsed metastatic prostate cancer or talazoparib with enzalutamide? ☐ 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
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	nil

8. What is the main aim of treatment for untreated hormone-relapsed metastatic prostate cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Prolong overall survival, reduce progression, maintain or improve QOL
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)	Significant overall survival benefit, particularly in the overall intention to treat population, rather than sub-gps.
10. In your view, is there an unmet need for patients and healthcare professionals in untreated hormone-relapsed metastatic prostate cancer?	Yes, patients invariably die of this disease. Progression can be rapid with current therapies.
11. How is untreated hormone-relapsed 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 talazoparib with enzalutamide have on the current pathway of care? • Would talazoparib with enzalutamide be offered to the same population who can get enzalutamide monotherapy or abiraterone with prednisolone? • Is there a subgroup of patients who could be offered olaparib with abiraterone and prednisolone (or prednisone) but could not be offered enzalutamide, or abiraterone with prednisolone (or prednisone) • Would you expect combination therapy with poly-ADP ribose polymerase (PARP) inhibitors like talazoparib	NICE and ESMO guidance. Most clinicians would accept the use of an ARPI firstline if ARPI – naïve. Clinicians would also consider the use of PARPi monotherapy in BRCA + tumours or combination with Olaparib and abiraterone. My feeling is that abi/Olaparib use in BRCA – tumours would be very uncommon. Docetaxel chemo would be next line followed by cabazitaxel or radium 223. I suspect clinicians are largely aligned in practice but I don't have evidence of this apart from many discussions with clinicians at national meetings. Tala/enza would give another combination choice for men with mCRPC. I believe most centres now test for BRCA mutations. I'm not clear how many routinely test for HRR deficiency. The evidence support the use of tala/enza in all-comers (primary end-pt) but there is a greater magnitude of benefit in HRR deficient, especially BRCA mutant cancers so clinicians may well use this for discussion with patients when a treatment decision is being made, given that the combination has side-effects. I don't think the population would be entirely the same. The tala/enza population is likely to be selected as asymptomatic/minimally symptomatic and generally fitter. They would have to be willing to accept the increased risk of haemtological toxicity especially anaemia which could require transfusion and fatigue. The

and olaparib to be offered to a homologous recombination repair (HRR) non-deficient tumour population on the NHS?	subgroup for ola/abi but not tala/enza is likely to be small, perhaps men with a history of seizures or very concerned about fatigue and cognitive effects of enza. I think tala/enza should be approved for all-comers in the same way ola/abi has been approved. Clinicians can then decide whether to use it predominantly in HRR deficient cases or BRCA cases or all-comers. I think most will look for deficiency or BRCA mutation rather than treat all-comers, but the option to treat all-comers should exist based on the evidence.
12. Will the talazoparib with enzalutamide be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between talazoparib with enzalutamide and current care? • In what clinical setting should talazoparib with enzalutamide be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce talazoparib with enzalutamide? (for example, for facilities, equipment, or training)	It is similar, but tala will require more monitoring in initial months due to the risk of anaemia. Transfusion requirements are likely to increase. It will be used in dedicated SACT clinics in the UK. I don't think too much investment is required, these clinics are set-up to deliver these sorts of treatments and most clinicians will already have experience with Olaparib.
13. Do you expect talazoparib with enzalutamide to provide clinically meaningful benefits compared with current care? • Do you expect talazoparib with enzalutamide to increase length of life more than current care? • Do you expect talazoparib with enzalutamide to increase health-related quality of life more than current care?	Yes, the combination extended OS from 37 to 45.8 months (HR 0.796). The to deteoriation of QOL was longer with tala/enza than with enza alone.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? • Would you expect the clinical outcomes to be different based on homologous recombination repair (HRR) gene alteration status (HRR deficient versus HRR non-deficient)? • If yes, how would the outcomes differ?	Yes, the magnitude of benefit is greater if HRR deficient (HR OS 0.54 vs 0.87).
15. Will talazoparib with enzalutamide 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)	It will be more difficult due to high rates of grade 3+ anaemia which may require treatment interruption and transfusion. This is manageable within UK SACT clinics, but I think will lead to careful patient selection eg. patients with haemoglobin on 9 or greater could enter the trial, I don't think this will be the case in the real world, so toxicity may be less in the real world.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I think most centres will test, but an argument could be made for treating all comers, although I believe this will be unusual.
17. Do you consider that the use of talazoparib with enzalutamide 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	Both tala and enza are oral which is an advantage. It significantly delays time to cytotoxic chemotherapy and many patients feel this is very important.

18. Do you consider talazoparib with enzalutamide 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?	Not a step change, but provides the best evidence for the use of a PARPi/ARPI combination to date and the median OS we are seeing ~ 47 months is better than we have seen to date so it does move the envelope.
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?	
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? • 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?	I think they broadly do although only 6% of patients had an ARPI prior to developing mCRPC, this is likely to be higher in the UK now. OS is most important and is positive. QOL is maintained or improved.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No, the OS data presented at GU ASCO in Feb 2025, I don't believe it is published yet, but it is very important for this submission.
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of the following NICE technology appraisal guidance? • **Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated [TA377]**	No

• Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated [TA387] • Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [TA951]	
23. How do data on real-world experience compare with the trial data?	Not aware of any
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 untreated hormone-relapsed metastatic prostate cancer and this treatment? Please explain if you think any groups of people with untreated hormone-relapsed metastatic prostate cancer 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 • 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.	

Part 2: Key messages

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

The combination of tala/enza significantly improves OS in an all-comer population with mCRPC

The effect appears to exist even in HRR proficient populations but is greater in HRR deficiency and greatest in BRCA loss.

Ideally UK centres would test for HRR deficiency and BRCA.

Anaemia was an issue in the trial leading to dose reduction, PARPi cessation (8%) and transfusions (40% I believe)

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Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

A Single Technology Appraisal

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

Alex Allen	Project manager. Lead for EAG's critical appraisal of the clinical evidence, writing and editorial input.
Dawn Lee	Lead for EAG's critical appraisal of the economic evidence and analysis. Drafted sections of the report.
Ahmed Abdelsabour	Critical appraisal of the economic evidence. Drafted sections of the report
Sophie Robinson	Lead for EAG's critical appraisal of the search strategy and drafted sections of the report.
Charlotte R Kelman	Critical appraisal of the clinical evidence. Drafted sections of the report.
Dr Matthew Fittall	Expert clinical advice to the EAG about metastatic castration-resistant prostate cancer and its treatment
Mr William Cross	Expert clinical advice to the EAG about metastatic castration-resistant prostate cancer and its treatment
G.J. Melendez-Torres	Project director and guarantor. Critical appraisal of the company submission, writing and editorial input.

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Abbreviations

Term	Definition
ADT	Androgen deprivation therapy
AE	adverse event
AR	Androgen receptor
ARPi	androgen receptor pathway inhibitors
ATX	Ataxia-telangiectasia mutated
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CRPC	castration-resistant prostate cancer
CS	company submission
CT	Computed tomography
CTC	Circulating tumour cells
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EAG	External Assessment Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate 25
EQ-5D-5L	EuroQol five dimension (five level)
FACT-P	Functional Assessment of Cancer Therapy Prostate Cancer
HRQoL	health-related quality of life
HRR	Homologous recombination repair
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ITT	Intention-to-treat
mCRPC	Metastatic castration-resistant prostate cancer
MHRA	Medicines and Healthcare products Regulatory Agency
NA	not applicable
NHA	Novel hormonal agent
NHS	National Health Service

Term	Definition
NHT	Novel hormonal therapy
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
NR	not reported
ORR	Objective response rate
OS	Overall survival
OWSA	one-way sensitivity analysis
PARP	Poly ADP ribose polymerases
PAS	Patient-access scheme
PFS2	time to second progression or death
PRO	patient reported outcomes
PSA	prostate-specific antigen
QA	quality assessment
QALY	quality adjusted life year
RCT	randomised controlled trial
rPFS	radiographic progression-free survival
SD	standard deviation
SLR	systematic literature review
TA	Technology Appraisal
TFST	time to first subsequent anticancer therapy or death
vs	Versus
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs). Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, 1.4, 1.5, and 1.6.

Broadly speaking the key clinical issues related to relevant comparators in the CS and the ITCs presented. In terms of cost effectiveness issues, there were a number of modelling assumptions that did not appear to be well founded given the evidence-base and clinical input received by the EAG.

Table 1: Summary of key issues

ID	Summary of issue	Report sections
Key Issue 1	Relevant comparators were not assessed in the submission	2.3.5, 2.3.6, and 2.4.2
Key Issue 2	Uncertainty related to the ITCs presented	3.3.2, 3.4.2, and 3.4.3
Key Issue 2	Assumption that time on treatment is equal to rPFS for olaparib with abiraterone but is lower for talazoparib with enzalutamide	4.2.6.3
Key Issue 4	Assumptions made post progression	4.2.7.1 and 4.2.6.4
Key Issue 5	Real-world use of PARP inhibitors may be limited to people with HRR deficient tumours	2.3.4 and 3.2.3.2

Abbreviations: HRR, homologous recombination repair; ITC, indirect treatment comparison; PARP, Poly(ADP-ribose) polymerase; rPFS, radiographic progression-free survival.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
TTD for olaparib with abiraterone	Same as rPFS (which implies longer TTD than for talazoparib with enzalutamide)	Adjust TTD using comparison of time dependent hazards for rPFS	4.2.6.3 and 6.2.1
Post progression utility	Historical literature used in TA377 from a variety of sources including non-reference case analyses	TA951 (from PROpel)	4.2.7.1 and 6.2.2
Drug wastage	Costs for the exact number of tablets used in a cycle	Drugs dosed as full packs (company scenario)	4.2.8.1 and 6.2.4
Skeletal-related events	Included using historical pooled data for olaparib with abiraterone	Excluded	4.2.7.3 and 6.2.3
Terminal care costs	Included	Excluded (double counting with palliative care)	4.2.8.5 and 6.2.5

Abbreviations: EAG, external assessment group; rPFS, radiographic progression-free survival; TTD, time to discontinuation

1.2. Overview of key model outcomes

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

Overall, the technology was modelled to affect QALYs by:

- Increasing the time spent alive
- Increasing the time spent progression-free which results in increased quality of life
- Reducing the frequency of skeletal related events in the comparison with olaparib with abiraterone (minor impact)

Overall, the technology was modelled to affect costs by:

- Changing the cost of treatment whilst progression-free (direction not given as this depends upon confidential prices)
- Reducing the cost of second-line treatments and palliative care due to increased time spent progression-free (minor impact)
- Increasing the cost of disease monitoring and concomitant medications due to increased time spent alive (minor impact)
- Reducing the cost of skeletal related events in the comparison with olaparib with abiraterone (minor impact)

The modelling assumptions that had the greatest effect on the ICER were:

- The treatment compared to – in particular abiraterone is available as a generic and is considered to be of similar effectiveness to enzalutamide (the within trial comparator)
- The population in which the comparison to olaparib with abiraterone was made and the method used for that comparison
- The assumption made for time to discontinuation in the comparison to olaparib with abiraterone
- The assumption made for post progression utilities

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

Key Issue 1: Relevant comparators were not assessed in the submission

Report sections	**2.3.5, 2.3.6, 2.4.2, 4.2.4, 6.1.3**
Description of issue and why the EAG has identified it as important	The company have proposed positioning talazoparib with enzalutamide as a first-line systemic treatment for people with mCRPC for whom chemotherapy is not indicated and where olaparib with abiraterone[1] would otherwise be offered. It was not clear to the EAG's clinical experts what subgroup of people with mCRPC could be offered olaparib with abiraterone[1] but could not be offered enzalutamide, or abiraterone[1]. Therefore, it would not be clinically valid to make an optimised recommendation in-line with the company's suggestion.

Report sections	2.3.5, 2.3.6, 2.4.2, 4.2.4, 6.1.3
	Thus, there were three relevant comparators for this appraisal: olaparib with abiraterone[1], enzalutamide, and abiraterone[1]. The EAG were aware that abiraterone became a generic and considerably cheaper than the other two comparators. Therefore, the EAG considered comparison versus abiraterone[1] to be a key to understanding the cost-effectiveness of olaparib with abiraterone[1]. The EAG was also aware that enzalutamide would be coming off patent in 2026 and that would be expected to considerably influence the results. Given the difference in prices of the drugs, and clinical expectation of similarity of effect, the cost-effectiveness results were very different against each of the comparators. Fully incremental could not be presented as the olaparib with abiraterone[1] comparison was in a different population to the enzalutamide comparison.
What alternative approach has the EAG suggested?	Comparison to all relevant treatments
What is the expected effect on the cost-effectiveness estimates?	At the time of writing, abiraterone was considerably cheaper than enzalutamide as it was available as a generic and enzalutamide was not. The EAG noted that the primary patent for enzalutamide in the UK is set to expire in 2026. The EAG-base case ICER using the cost of abiraterone in place of enzalutamide increased the ICER to [redacted] Scenario analysis assuming abiraterone was less effective than enzalutamide (HR = 1.19 applied to OS and rPFS) resulted in an ICER of [redacted]. In threshold analysis the EAG could not find a hazard ratio in which talazoparib with enzalutamide was cost-effective in the comparison to abiraterone using list prices for treatments other than talazoparib. Absolute QALYs were higher in the MAIC weighted population indicating that a comparison using the TALAPRO-2 population would be likely to be less favourable in the comparison with olaparib with abiraterone[1]. This was borne out in EAG scenario analysis using the original NMAs in the unweighted population which showed considerably reduced incremental QALYs.
What additional evidence or analyses might help to resolve this key issue?	None the EAG were aware of, given the limitations inherent in making the comparison to olaparib with abiraterone[1] and abiraterone[1].

Notes: [1] with prednisolone.
Abbreviations: EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; mCRPC, metastatic castration-resistant prostate cancer; NMA, network meta-analysis; STA, single Technology Appraisal.

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

Key Issue 2: Uncertainty related to the ITCs presented

Report sections	**3.3.2, 3.4.2, 3.4.3**
Description of issue and why the EAG has identified it as important	The company presented three types of ITC in the submission, but each type was subject to substantial uncertainty and the results were not similar enough to allay this uncertainty. The company presented two types of anchored NMA (PH NMAs and FP NMAs). Both were limited by a sparse network that used four comparisons across five studies to connect intervention and comparator. The company conducted PH NMAs within a Bayesian framework. However, the input data into the rPFS and OS NMAs did not meet the PH assumption and violating the PH assumption can lead to biased estimates and inaccurate conclusions. The company also presented a FP NMA as a clarification response (A6). They found no FP model was deemed suitable for OS. A suitable model was found for rPFS. It had the lowest DIC (p = -1), and the EAG questioned the extent of the validation undertaken with respect to other sources to complement this criterion in selecting an optimal fit. The company submitted an unanchored MAIC analysis. This addressed the EAG's concerns around the sparsity of the network but had its own set of limitations (Sections 3.3.2.1 and 3.3.2.2) linked to differences in eligibility criteria between **TALAPRO-2** and **PROpel**, and the inability to adjust for the most important prognostic factor. The lack of similarity between the PH NMA and the MAIC is detailed in Section 3.4.3 and the limitations of the time-varying HRs produced by the FP NMA in Section 3.4.2. Therefore, each of the ITCs submitted offered a different estimate of effect for the efficacy of talazoparib with enzalutamide versus olaparib with abiraterone for rPFS and OS, and each had substantial uncertainty/flaws. The EAG considered the unanchored MAIC to be the most appropriate ITC.
What alternative approach has the EAG suggested?	Given the uncertainty in the comparison with olaparib with abiraterone the EAG considered the demonstration of cost-effectiveness versus enzalutamide to be critical to validate the plausibility of results. This comparison was not subject to the same level of uncertainty as head-to-head data were available.
What is the expected effect on the cost-effectiveness estimates?	The ICER for the comparison to enzalutamide (not including discounts other than talazoparib) was [redacted] in the comparison to olaparib with abiraterone ([redacted] vs [redacted] in the EAG base case). QALY gains increased from [redacted] to [redacted] in this comparison.
What additional evidence or analyses might help to resolve this key issue?	Head-to-head trials comparing PARP inhibitor combinations. The EAG are not aware of any planned.

Abbreviations: DSU, decision support unit; EAG, External Assessment Group; FP, fractional polynomials; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, Matching-Adjusted Indirect Comparison; mCRPC, metastatic castration-resistant prostate cancer; NMA, network meta-analysis; OS, overall survival; PH, proportional hazards; rPFS, radiographic progression-free survival.

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 3: Assumption that time on treatment is equal to rPFS for olaparib with abiraterone but is lower for talazoparib with enzalutamide

Report sections	**4.2.6.3**
Description of issue and why the EAG has identified it as important	The company assumes the TTD is considerably lower than rPFS for talazoparib with enzalutamide resulting in a reduction in drug cost for talazoparib with enzalutamide of [redacted] This uses data from the unweighted patient population which has a lower rPFS than the MAIC weighted patient population introducing bias. Additionally, the company assumes that TTD and rPFS are the same for olaparib with abiraterone citing Clarke 2022 (the reference provided by the company for this abstract does not contain TTD data) and a prior CADTH appraisal which actually assumes TTD is lower than rPFS. This results in a mean time on first line treatment of [redacted] months for talazoparib as part of the combination compared to [redacted] for olaparib. Given that rPFS is shorter for olaparib this does not appear plausible. Clinical expert advice to the EAG was that the TTD / rPFS relationship would be expected to be similar for olaparib with abiraterone and talazoparib with enzalutamide. The EAG's experts also considered that in real-world practice they would not expect much difference between TTD and rPFS. The EAG consider that using TTD is more accurate than using rPFS as it appropriately captures the impact of patients stopping treatment due to reasons other than progression but that making different assumptions for the intervention and comparator is biased. These limitations do not apply in comparison to enzalutamide.
What alternative approach has the EAG suggested?	In the EAG base case we assume that the relationship between TTD and rPFS observed for talazoparib applies to olaparib and that the relationship between TTD and rPFS observed for enzalutamide applies to abiraterone. We present scenario analysis assuming TTD is equal to rPFS
What is the expected effect on the cost-effectiveness estimates?	On top of the EAG-corrected base case the difference in costs between talazoparib with enzalutamide and olaparib with abiraterone when only the talazoparib discount is included reduces from [redacted]
What additional evidence or analyses might help to resolve this key issue?	Additional data on the relationship between rPFS and TTD for olaparib with abiraterone.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; EAG, External Assessment Group; rPFS, radiographic progression-free survival; TTD, time to treatment discontinuation

Key Issue 4: Assumptions made post progression

Report sections	4.2.7.1 and 4.2.6.4
Description of issue and why the EAG has identified it as important	The company assumes that the utility post progression is 0.658 and 0.5 in palliative care (which represents the majority of time in the post progression health state). This is not in line with TA951 which assumed a much higher utility for the entire post progression state (0.775) or the majority of previous literature (a recent literature review found health-state utility values of 0.65 – 0.715). The assumption of lower utilities post progression benefits talazoparib with enzalutamide as this treatment increases the time spent progression-free and reduces the time spent post-progression. In addition, the company assumes that patients progress and enter palliative care immediately upon ceasing subsequent treatment which may not be appropriate for fixed duration treatments and the sources used for subsequent treatment duration are from a naïve targeted review and are often of lower quality. This interacts with the much lower utility value used for palliative care in the company model and relatively high palliative care costs.
What alternative approach has the EAG suggested?	The EAG use data which has now been supplied unredacted from TA951 for post progression utilities in our base case and data from a meta-analysis of utility values (Castro 2024) in sensitivity analysis. The EAG uses a constant utility value for the post progression state in the absence of a robust recent source for utilities in palliative care. The EAG provide scenario analysis reducing the time spent in palliative care to which palliative care costs are applied to test model sensitivity to the assumptions made.
What is the expected effect on the cost-effectiveness estimates?	On top of the EAG-corrected base case the difference in QALYs reduces from [redacted] to [redacted] when using the utilities from TA951.
What additional evidence or analyses might help to resolve this key issue?	Further information on the post progression utility in TALAPRO-2 could help although this may be of limited value due to the level of missing data.

Abbreviations: EAG, External Assessment Group.

1.6. Other key issues: summary of the EAG's views

Key Issue 5: Real-world use of PARP inhibitors may be limited to people with HRR deficient tumours

Report sections	2.3.4 and 3.2.3.2
Description of issue and why the EAG has identified it as important	Talazoparib and olaparib are both PARP inhibitors and PARP inhibitors were understood to be more effective in cancer cells that have HRR deficiency. The EAG's clinical experts stated that in their practices, olaparib with abiraterone was only offered to people with HRR deficient tumours and they expected to do the same with

Report sections	2.3.4 and 3.2.3.2
	talazoparib with enzalutamide, if a NICE recommendation were made. The company appeared to be aware of this and addressed the concern by noting research that suggested treatment with ARPis, could functionally impair HRR and this could potentially be exploited therapeutically by using combination therapy with PARP inhibitors.[1] Thus, talazoparib with enzalutamide could potentially be equally effective for people with mCRPC, irrespective of their tumour's HRR status. However, the EAG did not find evidence suggesting a synergistic effect between the therapies in subgroup analysis of rPFS in people whose tumours were HRR deficient and people whose tumours were non-deficient/unknown in **TALAPRO-2** (3.2.3.2). As reported in Section 3.2.3.2, the EAG compared the efficacy (rPFS and OS) in the intervention arms in Cohort 1 (21% HRR deficient) of **TALAPRO-2** and Cohort 2 (100% HHR deficient) of **TALAPRO-2**. The estimates of effect for rPFS and OS were [redacted] between Cohort 1 and Cohort 2 offering a signal of the synergistic effect between PARP inhibitors and ARPis. The EAG caveat this analysis with a warning that it was a naïve indirect comparison and, as such, was subject to a high risk of bias and uncertainty. This uncertainty was widened by unattributable differences in comparator efficacy between the cohorts.
What alternative approach has the EAG suggested?	Presentation of cost-effectiveness analysis by subgroup; particularly in comparison to enzalutamide.
What is the expected effect on the cost-effectiveness estimates?	Increased uncertainty in the comparison to enzalutamide. Direction of impact is unclear without subgroup specific analysis as greater effectiveness may be accompanied by a greater time on treatment.
What additional evidence or analyses might help to resolve this key issue?	Presentation of cost-effectiveness analysis by subgroup; particularly in comparison to enzalutamide.

Abbreviations: ARPis, Androgen Receptor Pathway Inhibitors; EAG, External Assessment Group; HRR, homologous recombination repair; OS, overall survival; PARP, Poly(ADP-ribose) polymerase; rPFS, radiographic progression-free survival.

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG's preferred assumptions reduced the cost difference between olaparib with abiraterone and talazoparib with enzalutamide from [redacted] in the corrected company base case to [redacted] in the EAG base case (confidential discounts only included for talazoparib). The QALY gain reduces from [redacted] to [redacted]. The main driver of the cost differences is the assumptions made for TTD. The main driver of the QALY differences is the utility assumed post progression.

The cost difference between enzalutamide monotherapy and talazoparib with enzalutamide increases marginally from [redacted] in the corrected company base case to [redacted] in the EAG base

case. The QALY gain reduces from [redacted] to [redacted]. The main driver of the differences is the assumptions made for the utility assumed post progression.

The ICER increases considerably in the EAG base case comparison to abiraterone due to the lower drug costs associated with this treatment. The ICER also increases considerably in the comparison to olaparib with abiraterone in scenarios using the unweighted population and either the FP NMA or PH NMA.

Table 3: Summary of EAG's preferred assumptions (confidential discount only included for talazoparib)

Scenario	Incremental cost	Incremental QALYs	ICER	iNMB (WTP £30k per QALY)
Comparison to olaparib with abiraterone				
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case*	[redacted]	[redacted]	[redacted]	[redacted]
Post progression utility from TA951	[redacted]	[redacted]	[redacted]	[redacted]
Drug wastage fully applied	[redacted]	[redacted]	[redacted]	[redacted]
Exclude SREs	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care cost excluded	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted TTD using comparative rPFS	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]
Comparison to enzalutamide				
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case*	[redacted]	[redacted]	[redacted]	[redacted]
Post progression utility from TA951	[redacted]	[redacted]	[redacted]	[redacted]
Drug wastage fully applied	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care cost excluded	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma OS	[redacted]	[redacted]	[redacted]	[redacted]
Gamma rPFS	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]
Comparison to abiraterone				
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case*	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; iNMB, incremental net monetary benefit; QALY, quality adjusted life year; WTP, willingness to pay

* Updated cabazitaxel and Radium-223 to use eMIT and corrected inflation for end-of-life costs

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by Pfizer for talazoparib with enzalutamide for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated. The company submitted a fully incremental cost-utility analysis (CUA) comparing talazoparib with enzalutamide to olaparib with abiraterone (and prednisolone), building on the previous cost comparison. However, as noted in Section 2.3.6, these were not the only relevant comparators identified by the EAG, which also included enzalutamide and abiraterone with prednisone/prednisolone.

A note on the formatting of the report, when people are treated with abiraterone, it is always given concomitant with prednisone or prednisolone. In the interest of conciseness, the EAG have not followed *abiraterone* with the phrase *with prednisone or prednisolone* in every case. Also, the EAG were aware that at the time of writing prednisone was not available through the NHS and therefore prednisolone is the relevant treatment in the NHS context. The EAG have specified prednisolone, rather than prednisone, where pertinent.

2.2. Critique of the company's description of the underlying health problem

The company presented its description of mCRPC in Section B.1.3.1 of the CS. The EAG considered the company's description to be mostly accurate. Prostate cancer is a condition where tumours develop in the prostate, a gland in the reproductive system.[2] [3] The exact cause remains unclear, though both environmental and genetic factors have been linked to a higher risk of developing prostate cancer.[2,4]

2.2.1. Prostate cancer

Prostate cancer was the most common and most frequently diagnosed form of cancer in people who have prostates in the UK in 2020.[5] The CS reported that there are approximately 55,100 new prostate cancer cases annually in the UK, of which 13% presented with metastatic disease at diagnosis. These data were true as of 2017-2019.[6] 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.[7] Between 2017-2019, there were approximately 12,000 prostate cancer deaths in the UK each year.[6]

2.2.2. Demographic risk factors

Prostate cancer risk increases significantly with age, affecting about 1 in 6 men overall.[8] However, it disproportionately impacts Black people, with around 1 in 4 diagnosed in their lifetime. Clinical experts informed the EAG that Black people are twice as likely than white people to develop the disease, probably due to heritable factors. Diagnosis in Black people 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.

According to the CS, prostate cancer is further 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 castration-sensitive prostate cancer (CSPC) or hormone-sensitive prostate cancer (HSPC). It may eventually become resistant to hormone therapy and is referred to interchangeably as castration-resistant prostate cancer (CRPC) or hormone-resistant prostate cancer (HRPC).[2] Prostate cancer can be localised disease, locally advanced disease, and metastatic disease, where the cancer has spread to distant sites in the body. This appraisal is in people whose cancer is castration/hormone resistant and has spread to distant sites in the body (metastatic) and is referred to as mCRPC from this point onwards.

The CS gave a good summary of the prevalence of mCRPC. The estimated prevalence of mCRPC was 1.2% among overall prostate cancer cases. This was the case from 1998 to 2009.[9] [10] As identified in the CS, mCRPC is an incurable, treatment-resistant cancer, with the main treatment goal being to extend survival and preserve health-related quality of life (HRQoL).[11]

2.3. Critique of the company's overview of current service provision

The company presented an overview of current service provision for mCRPC in Section B.1.3.2. The company cited treatment guidelines for the management of mCRPC, including NICE (NG131) and the European Society of Medical Oncology (ESMO)[12,13]. The company's depiction of the current care pathway is shown in Figure 1 in Document B.

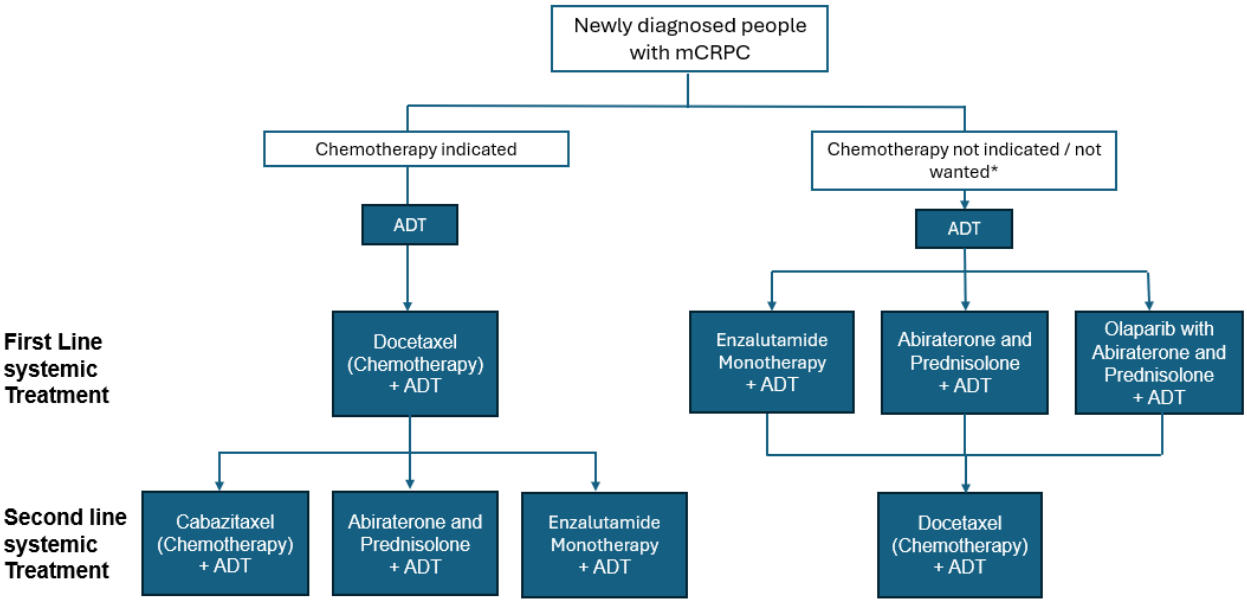
2.3.1. Service provision and eligibility for chemotherapy

The company depicted current service provision to be contingent on whether chemotherapy is indicated. People who are indicated for chemotherapy have docetaxel first line, and people who are not receive androgen receptor pathway inhibitor (ARPi) based treatment first line. However, the EAG's clinical experts stated that current service provision is no longer contingent on whether chemotherapy is indicated. Clinicians are now likely to offer ARPi based treatment to people who are eligible for chemotherapy in the first line mCRPC setting.

This was reflected in changes in standard of care in people with CSPC, where even in people deemed fit for chemotherapy, clinicians often prioritised offering people ARPis.[14] A study found from April to December 2020, the use of docetaxel for metastatic CSPC fell by 74%, while enzalutamide increased.

The EAG's clinical experts also noted that re-treatment with ARPis is not permitted in the NHS. As noted above, a proportion of people have ARPi treatment in the mCSPC setting, and as such, would not be eligible for ARPi or ARPi with PARP inhibitor combination treatment in the mCRPC setting.

Figure 1: Current treatment pathway for mCRPC



* People who are eligible for chemotherapy may instead choose to have ARPis.

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen deprivation therapy.

2.3.2. Androgen Deprivation Therapy (ADT)

In metastatic cases people are given ADT.[2] ADT works by reducing testosterone levels through surgical (bilateral orchiectomy) or chemical means.[15] Clinical experts noted that ADT is commonly viewed as the initial treatment, with any additional therapies, such as ARPis, considered part of the first-line systemic treatment.

Prostate cancer is sensitive to male androgens (i.e., male sex hormones) such as testosterone, and relies on the activation of androgen receptors to grow and survive.[16] Clinical experts informed the EAG that ADT reduces testosterone production by about 95% by targeting the testicles. The remaining 5% comes from the adrenal glands and cancer cells. The European Association of Urology (EAU) stated that patients with mCRPC should indefinitely continue ADT.[17] In line with this, clinical experts stated that in most cases ADT is not stopped except in the very terminal phase.

2.3.3. Androgen Receptor Pathway Inhibitors (ARPis)

If ADT alone fails, ARPis are recommended for those where docetaxel is not indicated or wanted.[18] ARPis refer to recently developed medicines which decrease androgen levels.[2] These include apalutamide, enzalutamide, darolutamide and abiraterone. ARPis are also known as new or novel hormonal agents (NHAs). The company used both, but the EAG will refer to these as ARPis as directed by clinical experts. First-line treatment options for people with mCRPC who are not candidates for chemotherapy include enzalutamide (TA377), abiraterone (TA387), and, since February 2024, the combination of olaparib with abiraterone (TA951). Clinical experts noted that ARPis have an additive effect on ADT, as there is continued low-grade androgen production from both the adrenal glands and the cancer cells themselves. The cancer sustains itself through this androgen production. ADTs reduce androgen levels in the body which the cancer cells need to grow, while ARPis further block the androgen receptor, preventing its activation and leading to cell death. This dual mechanism enhances the therapeutic effect.

Enzalutamide was recommended for treating hormone-relapsed metastatic prostate cancer in people whose ADT has failed and before chemotherapy is indicated.[2] Abiraterone, when used in combination with prednisone or prednisolone, was recommended for treating hormone-relapsed metastatic prostate cancer in patients with no or mild symptoms after ADT failure and before chemotherapy becomes necessary. Additionally, the combination of olaparib with abiraterone

and prednisone or prednisolone was recommended for adults who are unable to undergo chemotherapy or do not want it (TA951).[18]

2.3.4. PARP inhibitors

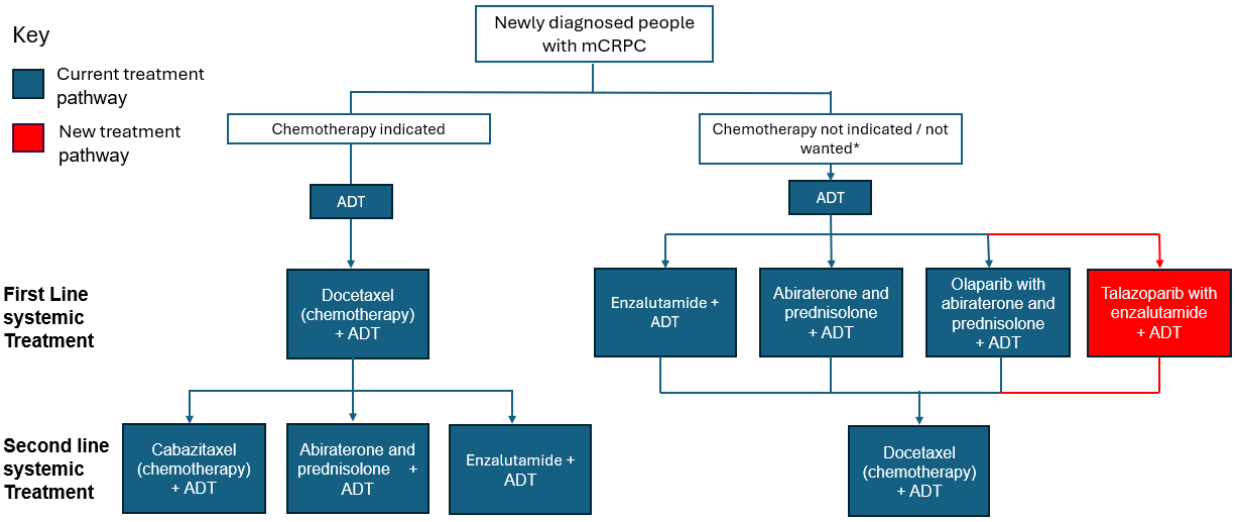
Talazoparib is a PARP inhibitor. PARP inhibitors work by blocking the action of an enzyme called human poly ADP ribose polymerase, which helps to repair damaged DNA in normal and cancer cells during cell division. When PARP is blocked, the damaged DNA in cancer cells cannot be repaired and, as a result, the cancer cells die. Cancer cells with homologous recombination repair (HRR) deficiency, such as the BRCA1 or BRCA2 mutations, rely more heavily on PARP to repair their DNA and continue dividing. Therefore, PARP inhibitors are understood to be more effective in cancer cells that have HRR deficiency. About 20-30% of people with mCRPC have cancer cells that have HRR deficiency.[19]

In Table 2 in Document B of the CS, the company noted the proposed synergistic effect when PARP inhibitors and ARPis such as enzalutamide and abiraterone, are used in combination. Research undertaken by Asim et al. (2017) suggested that ADT, including ARPis, could functionally impair HRR and this could potentially be exploited therapeutically by using combination therapy with PARP inhibitors.[1] However, despite the proposed synergistic effect the EAG's clinical experts stated that it was unlikely PARP inhibitors would be offered to people with HRR non-deficient tumours in their practices.

2.3.5. Positioning of talazoparib with enzalutamide

The company proposed talazoparib with enzalutamide as a first line systemic treatment for people with mCRPC where chemotherapy is not indicated, as an alternative to olaparib with abiraterone, enzalutamide, and abiraterone and prednisolone (Figure 2). At the clarification stage (B2), the company stated that they would be willing to accept a recommendation where talazoparib would be recommended in people to whom olaparib with abiraterone would otherwise be offered. The company explained that this would mean a comparison versus enzalutamide would not be necessary. However, it was not clear to the EAG's clinical experts what subgroup of people with mCRPC could be offered olaparib with abiraterone but could not be offered enzalutamide. Therefore, it would not be clinically valid to make an optimised recommendation in-line with the company's suggestion.

Figure 2: Proposed treatment pathway for mCRPC



* People who are eligible for chemotherapy may instead choose to have ARPis.
Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen deprivation therapy.

2.3.6. Comparability of intervention with comparators

While olaparib plus abiraterone has recently been recommended by NICE (TA951[18]) for people with mCRPC who cannot have or do not want chemotherapy, this comparator may not fully reflect standard clinical practice for the broader "no chemotherapy" population. Enzalutamide, and abiraterone with prednisolone were also first-line treatments for people with mCRPC and each had a larger market share at the time of writing. Across the last three quarters (June 2024 to February 2025), annualised CRPC pre-chemotherapy registrations ranged from 2,440 to 2,700. Enzalutamide consistently led market share, ranging from 50% to 56%, abiraterone followed with 31% to 38%, and olaparib with abiraterone at 12% to 15%. These data were provided by Peter Clark, the Cancer Drugs Fund Lead. It was not clear to the EAG whether olaparib with abiraterone would continue to have a smaller market share because, as stated by the EAG's experts, in their practices it would only be offered to people mCRPC whose tumour was HRR deficient. Alternatively, its small market share in 2024 may be due to the recentness of the recommendation and the market share may increase over the next year.

Table 4: Comparability of intervention with current comparators

Comparison	Talazoparib with enzalutamide	Olaparib with abiraterone and prednisolone	Enzalutamide	Abiraterone and prednisolone
International non-proprietary name (Brand)	Talzenna (talazoparib) and Xtandi (enzalutamide)	Lynparza (olaparib) with Zytiga (abiraterone) and Prednesol (presnisolone)	Xtandi (enzalutamide)	Zytiga (abiraterone) and Prednesol (presnisolone)
Principle pharmacological action and therapeutic class	*Talazoparib* is a PARP inhibitor (2.3.4) *Enzalutamide* is an ARPi that blocks androgen binding, nuclear translocation, and DNA association, thereby reducing prostate cancer cell growth and inducing cell death.	*Olaparib* is a PARP inhibitor (2.3.4) *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.	*Enzalutamide* is an ARPi that blocks androgen binding, nuclear translocation, and DNA association, thereby reducing prostate cancer cell growth and inducing cell death.	*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[20]	Recommended dose: 0.5 mg talazoparib in combination with 160 mg enzalutamide once daily. *Talazoparib* dose can be reduced stepwise down to 0.1 mg once daily due to toxicity. Dose of enzalutamide can be reduced (120 mg or 80 mg) due to toxicity. People should be treated until disease progression	Recommended dose: 600 mg *Olaparib*, 1000 mg *abiraterone* once daily with *prednisone* 5 mg orally twice daily. *Olaparib* dose can be reduced stepwise down to 400 mg daily due to toxicity. Abiraterone can be reduced to 500 mg due to hepatotoxicity.	Recommended dose: Enzalutamide (160 mg/day). Dose can be reduced (120 mg or 80 mg) due to toxicity. People should be treated until disease progression or unacceptable toxicity occurs.	Abiraterone: For mCRPC, abiraterone acetate is used with 10 mg prednisone or prednisolone daily. Abiraterone can be reduced to 500 mg due to hepatotoxicity. People should be treated until disease progression or unacceptable toxicity occurs.

Comparison	Talazoparib with enzalutamide	Olaparib with abiraterone and prednisolone	Enzalutamide	Abiraterone and prednisolone
	or unacceptable toxicity occurs.	People should be treated until disease progression or unacceptable toxicity occurs.		
Proposed/approved indications	*Talazoparib with enzalutamide* is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.	*Olaparib with abiraterone and prednisone or prednisolone* is indicated in combination for the treatment of adults with mCRPC in whom chemotherapy is not clinically indicated.	*Enzalutamide* is indicated as monotherapy or in combination with ADT for the for the treatment of mCRPC and for the treatment of mCRPC whose disease has progressed on or after docetaxel therapy.	*Abiraterone acetate with prednisone* is indicated with for mCRPC after ADT in whom chemotherapy is not yet clinically indicated, and treatment of mCRPC in whose disease has progressed after a docetaxel-based chemotherapy regimen.
Toxicities (or other characteristics) that may result in differences in use	*Talazoparib*: examples include leukopenia, acute myeloid leukaemia and alopecia. *Enzalutamide*: hypertension, ischemic heart disease and seizures.	*Abiraterone*: examples include hepatotoxicity, sepsis and cardiac disorders. *Olaparib*: examples include leukopenia, thrombocytopenia and neutropenia. *Prednisolone:* examples include Kaposi's sarcoma, schizophrenia and epilepsy.	*Enzalutamide*: hypertension, ischemic heart disease and seizures.	*Abiraterone*: examples include hepatotoxicity, sepsis and cardiac disorders. *Prednisolone:* examples include Kaposi's sarcoma, schizophrenia and epilepsy.
Any differences that may result in different populations using the medicine	It may be more commonly offered to the HRR deficient subgroup. This combination does not require concomitant steroid treatment.	It may be more commonly offered to the HRR deficient subgroup. People unable to take steroids cannot use this therapy.	This therapy does not require concomitant steroid treatment.	People unable to take steroids cannot use this therapy.

Abbreviations ADT, androgen deprivation therapy; ARPi, androgen receptor pathway inhibitors; DNA, deoxyribonucleic acid; EAG, external assessment group; LHRH, luteinising hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; NICE, National Institute for Health and Care Excellence; PARP, poly-ADP ribose polymerase.

2.4. Critique of company's definition of decision problem

The company's decision problem, along with the EAG's critique of it, is shown in Table 5 below. The EAG adds further detail to specific issues with population and comparators below.

2.4.1. Population

The population in the final scope[2] issued by NICE was adults with mCRPC for whom chemotherapy is not clinically indicated. However, as noted in Section 2.3.1, there has been a shift from offering docetaxel to offering ARPis in the first line setting. The EAG's experts explained that there was clear evidence that docetaxel caused more significant, though transient, impairment of quality of life than treatment with ARPis. Also, patient choice is relevant here, as ARPis are less immunosuppressive, can be administered at home, and as such, may be preferred. Given this change in practice, the EAG considered the relevant population to be adults with mCRPC who cannot have, or do not want, chemotherapy.

However, as explained in Section 2.1 of the cost comparison External Assessment Report, the majority of participants recruited to **TALAPRO-2** were indicated for chemotherapy but instead chose to have either talazoparib with enzalutamide or enzalutamide.[21] Therefore, the participants in the pivotal trial matched the relevant population.

2.4.2. Comparator

The intervention and comparator assessed in the CS were in line with the final scope issued by NICE. The comparator in the final scope was olaparib with abiraterone and did not include the other two treatments at the same position in the treatment pathway: enzalutamide and abiraterone (with prednisone or prednisolone). These comparators were in the draft scope but were removed when this became a fast-track appraisal using a cost-comparison approach.

The company stated it was appropriate to remove the other comparators as olaparib with abiraterone was found to be cost effective compared to both enzalutamide and abiraterone (with prednisone or prednisolone) in TA951.[18] The company reasoned that if talazoparib with enzalutamide had similar effectiveness, safety and cost as olaparib with abiraterone, i.e. a cost comparison approach was appropriate, then given the prior decision by NICE (TA951), it would also be cost effective versus enzalutamide and abiraterone (with prednisolone). As outlined in the EAG's cost comparison report, the cost comparison approach to appraise talazoparib with enzalutamide versus olaparib with abiraterone was not considered appropriate as the evidence suggested differential efficacy, leading to increased intervention costs. Hence, the previous

reasoning to remove enzalutamide and abiraterone with prednisolone from the scope was no longer valid. Therefore, the EAG understood that both were now relevant comparators.

As noted in Section 2.3.6, enzalutamide had consistently led market share for first-line treatment of people with mCRPC, ranging from 50% to 56%, compared to abiraterone with 31% to 38%. Also, the EAG considered enzalutamide to be a key comparator as it appeared, in the company's NMA presented Document B to be similarly effective to olaparib with abiraterone. Analysis presented in the cost comparison clarification response (A6) found it was more effective than abiraterone for rPFS and similarly effective (small numerical benefit) for OS. In TA951 an assumption was made that enzalutamide and abiraterone had similar effectiveness on the basis of clinical expert input and similar OS within the NMA conducted for that appraisal. The EAG considered that in the limited timelines of an STA, requesting a model update for one additional comparator would be reasonable, and that comparator should be enzalutamide. Therefore, at the clarification stage (B2), the EAG requested that the company include a comparison to enzalutamide within the economic model. The EAG then produced a comparison to abiraterone assuming equal effectiveness to enzalutamide, using the same logic as TA951.

Table 5: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated	In line with scope	N/A	Given changes in practice from docetaxel to ARPis in the first line setting in mCRPC, the EAG considered the relevant population for this appraisal to be adults with mCRPC who cannot have, or do not want, chemotherapy. The EAG considered the participants recruited to TALAPRO-2 matched the updated population.
Intervention	Talazoparib in combination with enzalutamide	In line with scope	N/A	Appropriate
Comparator(s)	Olaparib with abiraterone (and prednisone or prednisolone)	Olaparib with abiraterone	Olaparib with abiraterone represents the only relevant comparator for this cost comparison submission. Although enzalutamide and abiraterone are also in the same position in the treatment pathway as talazoparib with enzalutamide and olaparib with abiraterone, they are not relevant to this cost comparison appraisal because olaparib with abiraterone was shown to be cost-	This project began as a cost-comparison appraisal, and for reasons specifically linked to the use of a cost-comparison approach, enzalutamide and abiraterone with prednisolone were removed as comparators from the final scope. However, the reasoning behind removing these two comparators from the scope was no longer valid in the context of an STA. At the clarification

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			effective against both enzalutamide and abiraterone in TA951. Given that talazoparib with enzalutamide provides similar or greater health benefits at similar or lower costs than olaparib with abiraterone, a comparison versus enzalutamide and abiraterone is therefore not required.	stage, the company provided a comparison to enzalutamide within the economic model.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	In line with scope	N/A	Each of these outcomes was presented for the TALAPRO-2 trial. The unanchored MAIC evaluated overall survival and rPFS. However, the MAIC did not evaluate adverse effects of treatment or health-related quality of life.
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	In line with scope	This original submission presented a cost comparison of talazoparib with enzalutamide versus olaparib with abiraterone (see Section B.4 of the CS for details). The updated addendum presents a cost-	Cost-utility analysis without fully incremental analysis as enzalutamide, abiraterone with prednisolone and docetaxel which were all in the NICE scope related to this topic as an STA were not included in the

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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. The economic modelling should include the cost associated with diagnostic testing for people with hormone-relapsed metastatic prostate cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		effectiveness analysis comparing to olaparib with abiraterone. As talazoparib with enzalutamide is licensed for all eligible adult patients with mCRPC in whom chemotherapy is not clinically indicated, regardless of biomarker status, no specific genetic testing is required.	model. The lack of inclusion of enzalutamide was considered most problematic. In addition the analysis used a combination of utilities for post-progression survival which included non-reference case sources. Otherwise, the analysis was in line with the NICE reference case. The economic model did not include the cost of diagnostic testing. The EAG considered this appropriate as this would not differ between intervention and comparators.

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**	**EAG comment**

Subgroups	If the evidence allows, the following subgroups should be considered:
	• HRR status including:
	  ○ BRCA1 and BRCA2
	  ○ ATM gene.
		None	Subgroup analyses were not presented in the economic analysis.	The EAG considered HRR status to be a valid subgroup. Subgroup analysis from TALAPRO-2 is presented in this report. Subgroup analyses were not presented in the economic analysis.

Special considerations including issues related to equity or equality	Not presented	Not presented	N/A	

Abbreviations ARPis, Androgen Receptor Pathway Inhibitors; EAG, external assessment group; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NICE, National Institute for Health and Care Excellence rPFS, radiographic progression-free survival.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a clinical systematic literature review (SLR) with the objective of identifying randomised control trials (RCTs) to inform an indirect treatment comparison (ITC) of first-line pharmacological therapies in people with asymptomatic or mildly symptomatic mCRPC. The SLR was originally conducted on 9th September 2021 and updated on February 17, 2022 and October 3, 2022, with the latest update conducted on 8th August 2024. In total, the original and updated searches in the SLR identified 220 records reporting on 49 unique RCTs.

The EAG conducted a further search for additional relevant studies using the methods set out in the CS, but did not find any further relevant studies. Overall, the EAG found the company's systematic literature review to be of reasonable quality and likely to have identified all relevant studies. An overview of the SLR methods used by the company and the EAG appraisal of these is shown in Table 6.

Table 6: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	SLR report, Appendix	The searches were well conducted with a good range of sources and were PRESS checked by the company. However, they have not been updated since August 2024 so any additional publications and trials since that date will not have been included in the SLR. The EAG carried out some targeted update searches, see Section 3.2.1 below.
Inclusion criteria	SLR report, Table 3.1	The inclusion/exclusion criteria were appropriate and in line with the scope.
Screening	SLR report, 3.2.5	Screening was well conducted. Records were independently reviewed by two reviewers at title/abstract and at full text. Reviewers documented their reasons for exclusion and any discrepancies between the two reviewers were resolved by consensus or were referred to and resolved by a third independent reviewer not involved in the study selection process.
Data extraction	SLR report, 3.2.6	Data extraction was conducted appropriately using MS Excel. It was performed by one reviewer and validated by a second independent reviewer to verify data accuracy.
Tool for quality assessment of	SLR report, 3.2.7	The company used the using the NICE Single Technology Appraisal Evidence Submission Checklist for assessment of risk of bias in RCTs.

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
included study or studies		
Evidence synthesis	SLR report, 3.2.8	The company conducted an unanchored MAIC to estimate the comparative efficacy of talazoparib with enzalutamide versus olaparib with abiraterone for mCRPC.

Abbreviations: CS, Company submission; EAG, External Assessment Group; MAIC, matching-adjusted indirect comparison; mCRPC, metastatic castration-resistant prostate cancer; MS, Microsoft; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review.

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

3.2.1. Studies included in the clinical effectiveness review

The submission comprised one pivotal trial (**TALAPRO-2**)[22] of talazoparib with enzalutamide versus placebo with enzalutamide.

The searches in the SLR were conducted in August 2024, therefore the EAG did some additional searches to update some aspects of these. A search in PubMed for publications concerning **TALAPRO-2** found 11 articles published since August 2024 [23-33] and a search for publications concerning the **PROpel** trial found two articles published since that date.[34,35] In addition the EAG searched clinicaltrials.gov for clinical trials and found 61 trials concerning olaparib and 24 concerning talazoparib; 20 of these trials were registered in 2023 or later, but none of these were considered relevant by the EAG.

3.2.2. Description and critique of the design of the studies

An overview of the methods used in the pivotal trial for talazoparib with enzalutamide (**TALAPRO-2**) is presented in Table 7.

Table 7: Summary of trial methodology

Study	TALAPRO-2: NCT03395197[22]
Location	287 sites in 26 countries in North America, Europe (including UK), Israel, South America, South Africa, and Asia-Pacific region.
Trial design	Randomised, double-blind, placebo-controlled, Phase 3 study
Number of participants	N=805 (cohort 1[a])
Population	Adults with mCRPC
Interventions evaluated	Talazoparib (0.5 mg/day) + enzalutamide (160mg/day) vs Placebo + enzalutamide (160mg/day)
Concomitant medication	Permitted: bisphosphonates or denosumab, ADT, hematopoietic growth factors, ESAs or RBC transfusions.
Primary outcomes	BICR-assessed rPFS or death
Key secondary outcomes	- Overall survival (OS) - Investigator-assessed rPFS - Overall response rate (ORR) - PSA response - Time to confirmed PSA progression - Quality of life using EQ-5D-5L - Cancer-specific global health status/QoL, functional scales, and symptom scales (EORTC-QLQ-C30) - Adverse events
Selected pre-planned subgroups	- HRR status (HRR deficient and HRR non-deficient / unknown) - Prior NHT/ARPi (yes, no) - Prior docetaxel (yes, no)

Abbreviations: ADT, androgen deprivation therapy; ARPi, androgen receptor pathway inhibitor; BICR, blinded independent central review; EQ-5D-5L, EuroQol five dimension (five level) ; EORTC-QLQ-C30 European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ESAs, erythropoietin Stimulating Agents; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHT, novel hormonal therapies; ORR, overall response rate; PSA, prostate specific antigen; rPFS, radiographic progression-free survival; RBC, red blood cells.

Note: [a] Cohort 1 were recruited to the trial and were not selected based on their HRR status.

3.2.2.1. Design of the study

TALAPRO-2 consisted of two parts: **Part 1** was open-label and non-randomised and evaluated safety, tolerability, and pharmacokinetics; **Part 2** was Phase 3, randomised, double-blind, and

placebo-controlled, and evaluated efficacy and safety. We concentrate on **Part 2** of **TALAPRO-2** in this appraisal and it will henceforth be referred to as **TALAPRO-2**. The company have reported the results of Cohort 1 in in **TALAPRO-2**. Cohort 1 were the "all-comers population" that included people irrespective of homologous recombination repair (HRR) gene alterations. Randomisation was stratified by HRR gene alteration status (deficient vs non-deficient or unknown), and they undertook subgroup analysis in people based on their tumour's HRR status.

The company reported the 16th August 2022 datacut in Document B but updated this to the final data cutoff (3rd September 2024) in the Addendum[36] submitted on 12th March 2025. The company did continue enrolment in **TALAPRO-2** (Cohort 2) where it was restricted to people with HRR gene alterations. The efficacy and safety data for Cohort 2 were not reported in the CS but the company presented rPFS, OS, and adverse events results from Cohort 2 in the STA clarification response (C1).

3.2.2.2. Population

Trial eligibility criteria

TALAPRO-2 recruited people with mCRPC with progressive disease and an ECOG performance status of 0 or 1. Participants were not permitted to have had prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state. The EAG's clinical experts considered the inclusion criteria to be appropriate and in line with other trials in this disease area.

Baseline characteristics

The company presented the baseline demographics and disease characteristics of the participants in **TALAPRO-2** in Table 6 in Document B. The EAG's clinical experts commented that the trial population was a reasonable reflection of the populations they see in their practice. One expert noted that the population in the trial may be slightly younger than the population he sees in his practice, but he did not consider this difference to be a treatment effect modifier that would benefit either arm. The trial was stratified by HRR gene alteration status and 21% of participants were HRR deficient.

3.2.2.3. Intervention

In **TALAPRO-2**, participants received oral talazoparib (0.5 mg/day) in combination with oral enzalutamide (160 mg/day). Participants with moderate renal impairment received a reduced dose of talazoparib (0.35mg/day) to account for the lower talazoparib clearance.

3.2.2.4. Comparator

In **TALAPRO-2**, participants received placebo in combination with oral enzalutamide (160 mg/day).

3.2.2.5. Outcomes

The relevant outcomes collected in the trial were:

- Radiographic progression-free survival (rPFS) by blinded independent central review (BICR): per RECIST 1.1 criteria for soft tissue and the PCWG-3 criteria for bone;
- Overall survival (OS): time from randomisation to death from any cause;
- Objective response rate (ORR): people with measurable soft tissue disease at baseline per RECIST 1.1;
- Prostate-specific antigen (PSA) response: 50% or greater;
- Time to confirmed PSA progression;
- Time from randomization to progression on second-line therapy (PFS2);
- Quality of life using EQ-5D-5L;
- Adverse events: including Grade ≥3 treatment emergent adverse events (TEAEs).

The trial also collected cancer-specific global health status/QoL, functional scales, and symptom scales (EORTC-QLQ-C30).

3.2.2.6. Definition of study groups

The company detailed the analysis sets in Section B.3.4.1 of the CS. This has been reproduced in Table 8, below.

Table 8: TALAPRO-2 Part 2 analysis sets (reproduced from Table 7, Document B)

Analysis set	Description	Applicable analysis
All-comers population	Participants unselected for HRR status enrolled in Cohort 1.	--
Intent-to-treat	All participants randomly assigned to double-blind study treatment in Part 2 whether or not treatment was administered.	Efficacy analyses Select baseline characteristics summaries
Safety population	All participants who received at least 1 dose of study treatment (talazoparib, placebo, or enzalutamide).	Safety analyses Select baseline characteristics summaries
PK population	All participants who received at least 1 dose of study treatment and provided an evaluable PK sample.	PK analyses
CTC evaluable population	All participants from the Safety Analysis set with a baseline CTC assessment and at least 1 post-baseline CTC assessment.	CTC analyses
PRO population	All participants from the ITT population who completed a baseline PRO assessment and had at least 1 post-baseline PRO assessment prior to the end of study.	PRO analyses

Abbreviations: CTC, Circulating tumour cells; HRR, Homologous recombination repair; ITT, Intention-to-treat; PK, Pharmacokinetics; PRO, Patient-reported outcomes.

3.2.2.7. Statistical analysis

The company presented details of statistical methods in Section 3.4.2 of Document B. This included details of the sample size and power calculations.

Time-to-event endpoints were compared between treatment arms using a stratified log-rank test. HRs and associated two-sided 95% CIs were estimated by a Cox proportional hazards model. Median time-to-event endpoints were estimated by the Kaplan-Meier method, and 95% CIs were based on the Brookmeyer-Crowley method.

For the subgroup analysis of rPFS (except for the BRCA status), the HR was based on an unstratified Cox model with treatment as the only covariate due to the small number of people in some of the subgroups.

3.2.2.8. Dropouts

The final disposition of people in the **TALAPRO-2** trial was presented in Figure 2 and Table 14.1.1.2.1 in the CSR.[37] The EAG has adapted these into Table 9, below.

Relatively few people ([redacted]) withdrew consent or were lost to follow-up during the study in each treatment arm. The company state (Table 8, Doc B) that missing data were not imputed, except for date of birth (if year of birth was available), date of last dose of study treatment, death date, date of start of follow-up cancer therapy, and adverse events. Given the low rate of missing data, the EAG consider this to be a reasonable approach. Discontinuations in Table 9 were reported for each treatment, i.e. discontinuations were reported separately for talazoparib and for enzalutamide in the talazoparib with enzalutamide treatment arm. Therefore, it was not clear how many people discontinued both treatments, and whether they were discontinued at the same time.

Overall, discontinuations were higher for placebo ([redacted]) than talazoparib ([redacted]). This difference was primarily due to higher disease progression ([redacted] versus [redacted]) and lack of benefit ([redacted] versus [redacted]). However, a higher proportion of people discontinued talazoparib than placebo due to adverse events ([redacted] versus [redacted]) indicating higher toxicity of the combination therapy.

Discontinuations of enzalutamide were higher in the placebo with enzalutamide arm ([redacted]) than the talazoparib with enzalutamide arm ([redacted]). Again, this was primarily due to disease progression and lack of benefit. However, discontinuations of enzalutamide due to adverse events were higher in the talazoparib with enzalutamide arm ([redacted] versus [redacted]), indicating higher toxicity of the combination therapy.

Discontinuations of either treatment in each arm due to a global deterioration of health were higher in the talazoparib with enzalutamide arm (talazoparib: [redacted]%, enzalutamide: [redacted]%) than the placebo with enzalutamide arm (placebo: [redacted]%, enzalutamide: [redacted]). It was unclear to the EAG whether this was a clinically meaningful difference, and to what extent this could be attributed to the treatments to which they were randomised.

Table 9: TALAPRO-2: participant disposition (adapted from Figure 2 and Table 14.1.1.2.1, CSR)

	Talazoparib with enzalutamide (n=398)		**Placebo with enzalutamide (n=401)**	
n (%)	Talazoparib	Enzalutamide	Placebo	Enzalutamide
Total discontinued	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow up	[redacted]	[redacted]	[redacted]	[redacted]

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
Disease progression	[redacted]	[redacted]	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]
Global deterioration of health	[redacted]	[redacted]	[redacted]	[redacted]
Lack of benefit	[redacted]	[redacted]	[redacted]	[redacted]
Other reason	[redacted]	[redacted]	[redacted]	[redacted]

3.2.2.9. Critical appraisal of the design of the studies

The company presented a critical appraisal of **TALAPRO-2** in Section B.3.5 of the CS using the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs on the NICE website.[38] In contrast to the critical appraisal of the studies in the NMA, the company did offer reasoning for their judgements made for each risk of bias criteria. No overall risk-of-bias judgement was stated but given the study was assessed to be at a low risk of bias for each criterium it was appropriate to conclude that the company judged **TALAPRO-2** to be at low risk of bias overall. While the EAG agreed that **TALAPRO-2** was a well conducted trial, the EAG had some concerns on the reporting of patient reported outcomes. It was unclear why the company only presented a key quality of life outcome, change in EQ-5D-5L index scores, as a graph. It would have been appropriate to present point estimates for the change in EQ-5D-5L index scores after one, two, three, and four years of treatment to allow a fuller critique of the results.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

The company presented evidence from the August 16th 2022 data cut for Cohort 1 of **TALAPRO-2** in Section 3.6 in Document B. In addition to the clinical evidence presented in Document B, the company also presented rPFS and OS from the 3rd September 2024 data cut in Section 1.1 of the Addendum. The EAG presented the results of the August 16th 2022 data cut in Section 3.4 of the cost comparison External Assessment Report (EAR)[21]. This second EAR concentrates on rPFS and OS from the 3rd September 2024 data cut (median follow-up: [redacted] months for the talazoparib arm, [redacted] months for the placebo arm).

Radiographic progression-free survival by BICR

At the 3rd September 2024 data cut, talazoparib with enzalutamide demonstrated a [redacted] in rPFS over placebo with enzalutamide (HR:[redacted]; 95% CI: [redacted]; p[redacted]). The probability (95% CI) of being event free at 48 months was [redacted] ([redacted] to [redacted] for people in the talazoparib with enzalutamide arm, and [redacted] ([redacted] to [redacted] for people in the placebo with enzalutamide arm (see Table 10).

At the clarification stage, the company presented blinded independent central review (BICR) assessed rPFS in Cohort 2 (all HRR positive) of **TALAPRO-2** (see Table 10). The results of the talazoparib with enzalutamide arm in Cohort 2 were [redacted] to the talazoparib with enzalutamide arm in Cohort 1. However, the results in the placebo with enzalutamide arm in Cohort 2 were [redacted] than the placebo with enzalutamide arm in Cohort 1. It was unclear to the EAG why the efficacy of the comparator was [redacted] between the two cohorts given that the only difference in recruitment between the cohorts was limiting Cohort 2 to people who were HRR deficient. While the EAG was concerned that the estimates of effectiveness in the comparator arms were [redacted] in each cohort, the EAG accepted that the efficacy of talazoparib with enzalutamide was [redacted] in a Cohort 1, where 21% of participants were HRR deficient, and Cohort 2, where 100% of participants were HRR deficient.

Table 10: TALAPRO-2: Summary of BICR-assessed rPFS for the Cohort 1 and Cohort 2 population at the 3rd September 2024 data cut (adapted from Table 1, Addendum and C1 STA clarification response)

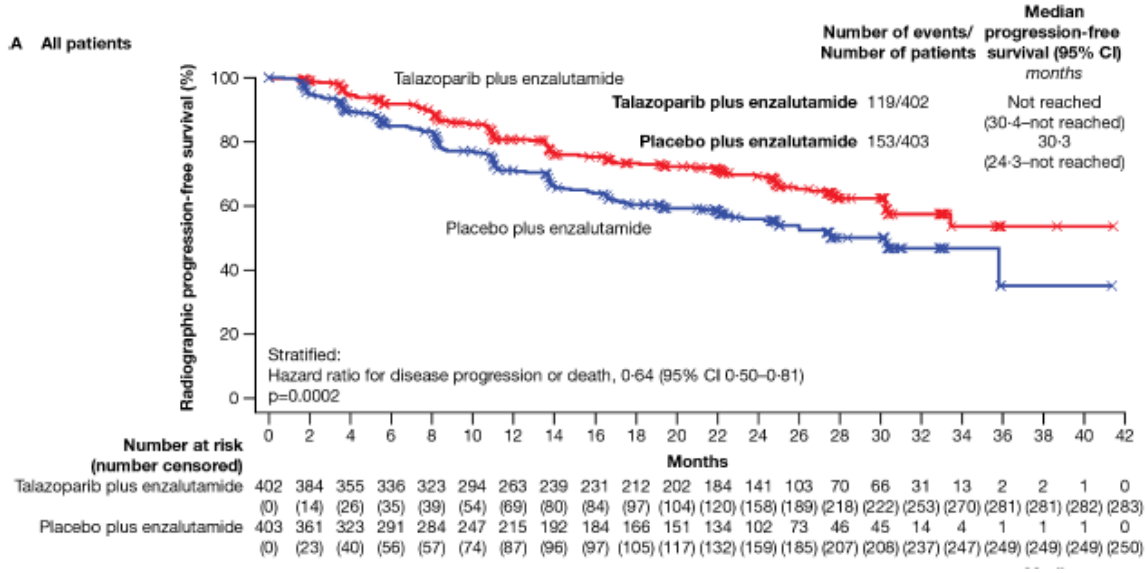
Cohort 1	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median rPFS by BICR, months (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]
Events (%)	[redacted]	[redacted]	--	--
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	--	--
24 months	[redacted]	[redacted]	--	--
36 months	[redacted]	[redacted]	--	--
48 months	[redacted]	[redacted]	--	--
Cohort 2	**Talazoparib with enzalutamide (n=200)**	**Placebo with enzalutamide (n=199)**	**Hazard ratio (95% CI)**	**2-sided p-value**
Median rPFS by BICR, months (95% CI)[a]	[redacted]	[redacted]	[redacted]	[redacted]

Cohort 1	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Events (%)	[redacted]	[redacted]		
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	--	--
24 months	[redacted]	[redacted]	--	--
36 months	[redacted]	[redacted]	--	--
48 months	[redacted]	[redacted]	--	--

[a] Based on the Brookmeyer-Crowley method.
[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.
Abbreviations: BICR, Blinded independent central review; CI, Confidence interval; ITT, Intention-to-treat; rPFS, Radiographic progression-free survival.

The EAG assessed the proportional hazards (PH) assumption for rPFS in Cohort 1 of **TALAPRO-2**. No log-log plots or Schoenfeld residuals were presented and the EAG used the Kaplan-Meier (KM) curve to visually assess the PH assumption (Figure 3). The EAG judged that the hazard ratio between groups does not remain constant over time and, as such, does not suggest proportionality.

Figure 3: Radiographic progression-free survival in all patients (adapted from Figure S1 in Agarwal et al. 2023)[22]



Abbreviations: CI, confidence interval.

Overall survival

At the 3rd September 2024 data cut, **TALAPRO-2** found a [redacted] for talazoparib with enzalutamide over placebo with enzalutamide in OS (HR: [redacted]; 95% CI: [redacted]; p[redacted]). The probability (95% CI) of being alive at 48 months was [redacted] ([redacted] to [redacted] for people in the talazoparib with enzalutamide arm, and [redacted] ([redacted] to [redacted] for people in the placebo with enzalutamide arm (see Table 11).

At the clarification stage (C1), the company presented efficacy results from Cohort 2 (HRR deficient). Similar to rPFS, the OS of the talazoparib with enzalutamide arm in Cohort 2 was [redacted] to the talazoparib with enzalutamide arm in Cohort 1. However, the OS in the placebo with enzalutamide arm in Cohort 2 was notably [redacted] than the placebo with enzalutamide arm in Cohort 1. While the EAG was concerned that the estimates of effectiveness in the comparator arms were [redacted] in each cohort, the EAG accepted that the efficacy of talazoparib with enzalutamide was [redacted] in Cohort 1, where 21% of participants were HRR deficient, and Cohort 2, where 100% of participants were HRR deficient.

Table 11: Summary of OS for the Cohort 1 and Cohort 2 population at the 3rd September 2024 data cut (adapted from Table 1, Addendum and C1 STA clarification response)

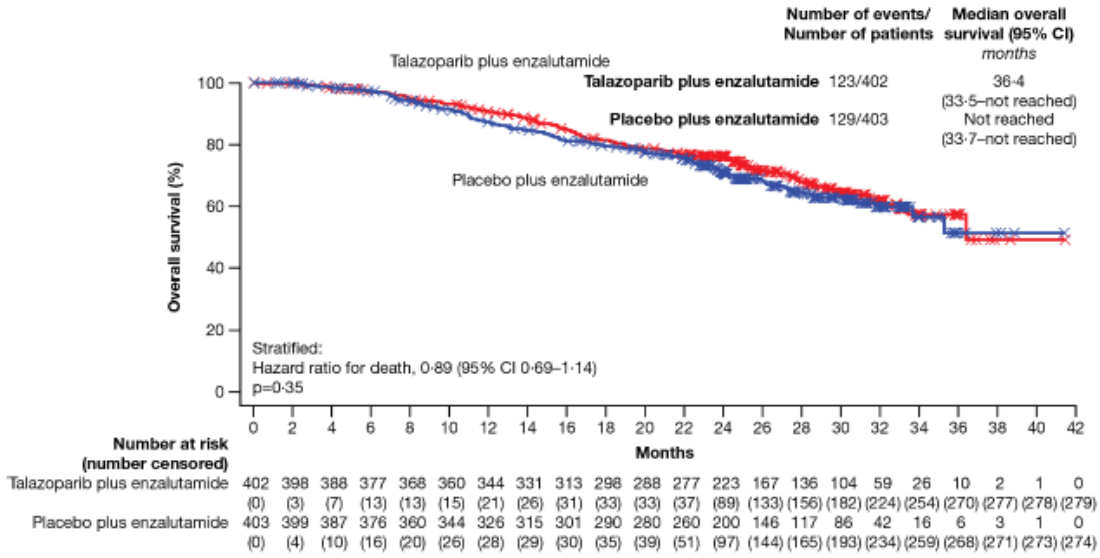
Cohort 1	**Talazoparib with enzalutamide (n=402)**	**Placebo with enzalutamide (n=403)**	**Hazard ratio (95% CI)**	**2-sided p-value**
Median[a] (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
Number of events n(%)	[redacted]	[redacted]	-	-
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	-	-
24 months	[redacted]	[redacted]	-	-
36 months	[redacted]	[redacted]	-	-
48 months	[redacted]	[redacted]	-	-
60 months	[redacted]	[redacted]	-	-
Cohort 2	Talazoparib with enzalutamide (n=200)	Placebo with enzalutamide (n=199)	Hazard ratio (95% CI)	2-sided p-value

Cohort 1	Talazoparib with enzalutamide (n=402)	Placebo with enzalutamide (n=403)	Hazard ratio (95% CI)	2-sided p-value
Median[a] (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
Number of events n(%)	[redacted]	[redacted]	-	-
Probability of being event-free[b] (95% CI)				
12 months	[redacted]	[redacted]	-	-
24 months	[redacted]	[redacted]	-	-
36 months	[redacted]	[redacted]	-	-
48 months	[redacted]	[redacted]	-	-
60 months	[redacted]	[redacted]	-	-

[a] Based on the Brookmeyer-Crowley method.
[b] CIs are derived using the log-log transformation with back transformation to untransformed scale.
Abbreviations: BICR, Blinded independent central review; CI, Confidence interval; ITT, Intention-to-treat; NE, not evaluable; rPFS, radiographic progression-free survival.

The EAG assessed the proportional hazards (PH) assumption for OS in **TALAPRO-2**. No log-log plots or Schoenfeld residuals were presented and the EAG used the Kaplan-Meier (KM) curve to visually assess the PH assumption (Figure 4). The EAG judged that the PH assumption was clearly violated as the KM curves crossed multiple times.

Figure 4: Overall survival in all patients in Cohort 1 of TALAPRO-2 (adapted from Figure S2 in Agarwal et al. 2023)[22]



Abbreviations: CI, confidence interval.

Results from the August 16th 2022 data cut

The results from the August 16th 2022 data cut, adapted from the previous EAR, are presented below in Table 12. At this earlier data cut, talazoparib with enzalutamide demonstrated a statistically significant benefit over placebo with enzalutamide for objective response, PSA response, time to PSA progression, and PFS2. There was no difference between treatment arms in time to first symptomatic skeletal event.

Table 12: Efficacy results from the August 16th 2022 data cut in the TALAPRO-2 trial (adapted from Table 5 in the cost comparison EAR)

	Talazoparib with enzalutamide (n=402)	**Placebo with enzalutamide (n=403)**	**Hazard ratio (95% CI)**	**p-value**
Objective response[b], n (%; 95% CI)	74 (61.6; 52.4, 70.4)	58 (43.9; 35.3, 52.8)	-	0.0050
PSA response ≥50%[c], n (%; 95% CI)	331 (83.6; 79.6-87.1)	284 (72.1; 67.4-76.5)	-	0.0001
Median time to PSA progression (95% CI), months	26.7 (21.2, 30.4)	17.5 (14.1, 20.8)	0.72 (0.58, 0.89)	0.0020
Median time to first symptomatic skeletal event (95% CI), months	NR (NR) Events: 91 (22.6%)	NR (NR) Events: 93 (23%)	0.88 (0.66, 1.18)	0.41
Median PFS2[d] (95% CI), months	36.4 (33.5, NR) Events: 126 (31.3%)	35.3 (28.6, NR) Events: 143 (35.5%)	0.77 (0.61, 0.98)	0.036

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CS, company submission; EAR, external assessment report; NMA, network meta-analysis; NR, not reported; OS, overall survival; PFS2, time from randomization to progression on second-line therapy; PSA, prostate specific antigen; RCT, randomised controlled trial.

Notes: [a] Based on the Brookmeyer-Crowley method; [b] Only includes patients with measurable soft tissue disease at baseline per BICR: talazoparib arm (n=120); placebo arm (n=132); [c] Only includes patients with a baseline PSA value and at least one post-baseline PSA value: talazoparib arm (n=396); placebo arm (n=394); [d] PFS2 based on investigator assessment (time from randomisation to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurs first).

3.2.3.2. Subgroup analyses

As noted in Section 2.3.4, PARP inhibitors such as talazoparib and olaparib, were known to be more effective in tumour cells that are HRR deficient and the NICE final scope stated that if the evidence allowed, the HRR status subgroup should be considered. The EAG's clinical experts

stated that they would not offer a PARP inhibitor to people who were HRR non-deficient, and as such, the EAG considered this subgroup analysis to be pertinent to this appraisal and could influence the uptake of the treatment within the NHS. Subgroup analysis was not presented in the CS but it was presented in Agarwal et al. 2023.[22] The HRR status subgroup (as per randomisation stratification) analysis using the primary outcome (rPFS) found:

- HRR deficient (n=169): HR: 0·46; 95% CI 0·30, 0·70; p=0.0003.
- HRR non-deficient or unknown (n=636): HR: 0·70; 95% CI 0·54, 0·89; p=0.0039.
- All people (n=805): HR 0.63; 95% CI: 0.51, 0.78, p<0.0001).

Talazoparib with enzalutamide had a statistically significant benefit over placebo with enzalutamide in people whose tumours were HRR deficient and people whose tumours were HRR non-deficient or unknown. However, a tumour's HRR status did appear to be a treatment effect modifier because the efficacy was reduced in people with HRR non-deficient or unknown tumours.

Subgroup analysis for OS was presented in Agarwal et al. 2025[39] using the 3rd September 2024 cutoff:

- HRR deficient (n=169): HR 0.55; 95% CI: 0.36, 0.83; p=0.0035).
- HRR non-deficient or unknown (n=636): HR 0.88; 95% CI: 0.71, 1.08; p=0.218).
- All people (n=805): HR 0.80; 95% CI: 0.66, 0.96; p=0.0155).

Talazoparib with enzalutamide had a statistically significant benefit over placebo in people whose tumours were HRR deficient but the benefit was numerical in people whose tumour was HRR non-deficient or unknown.

The EAG received additional relevant data on the efficacy of talazoparib with enzalutamide in the HRR deficient population at the clarification stage. As noted in Section 3.2.2.1, the company continued enrolment in **TALAPRO-2** with Cohort 2. Recruitment to Cohort 2 was restricted to people with HRR gene alterations (i.e. HRR deficient). The efficacy and safety data for Cohort 2 were not reported in the CS but the company presented rPFS and OS results in the STA clarification response (C1). The EAG compared the estimates of effect for the talazoparib with enzalutamide arms of Cohort 1 (21% confirmed HRR deficient) and Cohort 2 (100% confirmed

HRR deficient) for rPFS and OS in Section 3.2.3.1. It was notable to the EAG that the estimates of effect for rPFS and OS were [redacted] in the talazoparib with enzalutamide arms in Cohort 1 (21% HRR deficient) and Cohort 2 (100% HRR deficient). While this was a signal that there may be a synergistic effect between PARP inhibitors and ARPis (2.3.4), this was a naïve indirect comparison and, as such, was subject to a high risk of bias and uncertainty. Also, the comparator arms (placebo with enzalutamide) performed [redacted] in each cohort despite the only difference in eligibility criteria being HRR status. HRR status was not understood to be a treatment effect modifier for enzalutamide and there may be other differences between the participants in Cohort 1 and Cohort 2 that influenced the treatment effect.

3.2.3.3. Patient reported outcomes

No further patient reported outcomes (PROs) were presented in the company's Addendum and, as such, the EAG has reproduced the PRO critique from the cost comparison EAR.

Overall QoL was measured using EuroQol-5 dimensions-5 levels (EQ-5D-5L) and this was presented as a plot (Figure 5) rather than change score. The graph appeared to show [redacted]. However, the EAG maintain that it would have been appropriate to present the mean difference with standard deviation for the change in EQ-5D-5L from baseline until discontinuation of treatment during the trial.

The company also collected prostate cancer-specific QoL, as measured by EORTC-QLQ-PR25. Again, no point estimates were presented but the company stated that there was [redacted] across all functional and symptom scales, with [redacted] between the treatment arms.

Overall cancer-related QoL, as measured by EORTC-QLQ-C30, [redacted] functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) [redacted]. However, there were EORTC-QLQ-C30 symptom scales, with [redacted] for global health status/quality of life (GHS/QoL). These were fatigue, nausea/vomiting, dyspnoea, and appetite loss. The company stated that the [redacted] (as measured by a 10-point difference) [redacted] did not provide point estimates or interval data for the EAG to critique. The company did present the median time-to-definitive deterioration (TTDD) in GHS/QoL, which was [redacted] for the talazoparib arm than the placebo arm ([redacted] months vs [redacted] months; [redacted]).

Pain symptoms were measured using Brief Pain Inventory – Short Form (BPI-SF). There did [redacted] between the treatment arms but it was not clearly reported. Overall, poor reporting of the patient reported outcomes in the CS led to some uncertainty in the efficacy of talazoparib with enzalutamide versus placebo with enzalutamide. Better reporting would have also supported a more transparent comparison of patient reported outcomes in people treated with talazoparib with enzalutamide in the **TALAPRO-2** trial and people treated with olaparib with abiraterone in **PROpel**.

Figure 5: Plot of EQ-5D-5L index scores change from baseline in the Cohort 1 Part 2 PRO population (reproduced from Figure C, Doc B)

Abbreviations: . EQ-5D-5L, EuroQol five dimension (five level); PRO, patient reported outcomes

3.2.3.4. Safety

Extent of exposure

The duration of exposure to study drugs in **TALAPRO-2** is detailed below in Table 13. At the clarification stage, the company presented time to discontinuation (TTD) data for talazoparib with enzalutamide based on the latest data cut of **TALAPRO-2** (cutoff date 3rd September 2024). TTD is further explored in Section 4.2.6.3.

A summary of exposure to the study drugs for the Cohort 1 all-comers safety population is presented in Table 13. At the data cutoff date of 3rd September 2024 (median follow-up for the primary analysis: [redacted] months for the talazoparib arm, [redacted] months for the placebo arm), the mean duration of treatment was [redacted] weeks for talazoparib and [redacted] weeks for placebo, with a

mean relative dose intensity of [redacted]% and [redacted]%, respectively. The mean duration of enzalutamide treatment was [redacted] weeks in the talazoparib arm and [redacted] in the placebo arm. This reflects the slower progression of mCRPC in the intervention arm.

There were a substantially higher number of dose reductions for talazoparib than placebo, primarily [redacted] events. There were twice as many dose reductions ([redacted]% versus [redacted]%) of enzalutamide in the talazoparib arm compared to enzalutamide in the placebo arm. These were also primarily [redacted], but it was unclear to the EAG whether this was linked to interactions between talazoparib and enzalutamide, or whether it was a reflection of the [redacted].

Table 13: TALAPRO-2: Summary of the drug dosing exposure for the safety population (adapted from Tables 5 and 6, Addendum and Tables 13 and 14, CSR 2024)

	Talazoparib with enzalutamide	Placebo with enzalutamide	Total
Duration of treatment talazoparib/placebo,[a] weeks			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Relative dose intensity talazoparib/placebo[b] (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Dose reductions talazoparib/placebo, n (%)			
All	[redacted]	[redacted]	[redacted]
Due to AE	[redacted]	[redacted]	[redacted]
Due to other reasons	[redacted]	[redacted]	[redacted]
Duration of treatment enzalutamide,[a] weeks			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Relative dose intensity enzalutamide (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Dose reductions enzalutamide, n (%)			
All	[redacted]	[redacted]	[redacted]
Due to AE	[redacted]	[redacted]	[redacted]
Due to other reasons	[redacted]	[redacted]	[redacted]

[a] Treatment duration (weeks) is defined as (date of last dose – date of first dose +1)/7.
[b] Relative dose intensity (%) is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in %.
[c] Includes permanent discontinuation, dose reduction, or dose interruption of talazoparib or placebo with permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide.
Abbreviations: AE, Adverse event; SD, Standard deviation.

Adverse events

Talazoparib with enzalutamide demonstrated a substantially higher adverse event (AE) burden than placebo with enzalutamide. [redacted]percent of participants in the talazoparib with enzalutamide arm experienced a serious treatment-emergent adverse event (TEAE) compared with [redacted]% in the placebo with enzalutamide arm. The EAG's clinical experts stated that this level of toxicity would be expected for PARP inhibitor treatment. A [redacted] proportion of people discontinued talazoparib, a PARP inhibitor, than discontinued placebo, due to AEs ([redacted] versus [redacted]), while a [redacted] proportion in each arm discontinued enzalutamide due to AEs ([redacted] versus [redacted]).

The most common Grade ≥3 event was anaemia; this was experienced by [redacted] ([redacted]) of participants on talazoparib with enzalutamide and in [redacted] ([redacted]) participants on placebo with enzalutamide. While this was a high proportion of people in the intervention arm, the EAG's clinical expert noted that anaemia can develop over a number of months and can be corrected without a need to limit or interrupt their dose. Other grade ≥3 AEs that were notably higher in people on talazoparib with enzalutamide were neutrophil count decreased ([redacted] versus [redacted]), platelet count decreased ([redacted] versus [redacted]), white blood cell count decreased ([redacted] versus [redacted]), and lymphocyte count decreased ([redacted] versus [redacted]). More than [redacted] of participants on each treatment regime experienced grade ≥3 hypertension ([redacted] versus [redacted]). The EAG's clinical experts stated that it is important to make people aware of the medication toxicity and the efficacy of the treatment for them to support patient choice.

Table 14: Summary of AEs for the safety population (N=799) (adapted from Table 7, Addendum)

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any TEAE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5 TEAE (%)	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from study due to TEAE (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]
TEAE resulting in drug discontinuation (%)				
Talazoparib or placebo	[redacted]	[redacted]	[redacted]	[redacted]
Enzalutamide	[redacted]	[redacted]	[redacted]	[redacted]

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	Grade ≥3	All grades	Grade ≥3
Most common AE (Grade ≥3 in ≥5% of participants), n (%)				
Anaemia	[redacted]		[redacted]	
Neutrophil count decreased	[redacted]		[redacted]	
Platelet count decreased	[redacted]		[redacted]	
White blood cell count decreased	[redacted]		[redacted]	
Hypertension	[redacted]		[redacted]	
Lymphocyte count decreased	[redacted]		[redacted]	

Data are n(%). Shown are AEs that occurred from the time of the first dose of study treatment through to 28 days after permanent discontinuation of all study treatments or before initiation of a new antineoplastic or any investigational therapy, whichever occurred first. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[a] Participants who have an AE record that indicates that the AE caused the Participants to be discontinued from the study.

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Skeletal related events

Skeletal related events (SREs) were reported in Section 1.3.2 of the Addendum. SREs were reported [redacted] for participants in the talazoparib with enzalutamide treatment arm than for participants in the placebo with enzalutamide treatment arm.

Table 15: Summary of SREs for the safety population (N=799; reproduced from Table 8, Addendum)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)
Any SRE (%)	[redacted]	[redacted]
Non-symptomatic fracture (%)	[redacted]	[redacted]
Radiotherapy to bone (%)	[redacted]	[redacted]
Spinal cord compression (%)	[redacted]	[redacted]
Surgery to bone (%)	[redacted]	[redacted]
Symptomatic fracture (%)	[redacted]	[redacted]

Participants are only counted once per treatment event. MedDRA v25 coding dictionary applied.
Abbreviations: SRE, Skeletal related event.

3.3. Indirect treatment comparison

In Document B, the company presented an NMA, using a Cox proportional hazards model, comparing talazoparib with enzalutamide to olaparib with abiraterone for rPFS, OS, and time to PSA progression. The additional interventions used to make the network were abiraterone, enzalutamide, and best supportive care (BSC). The EAG presented a full critique of this NMA in the cost comparison EAR report.[21]

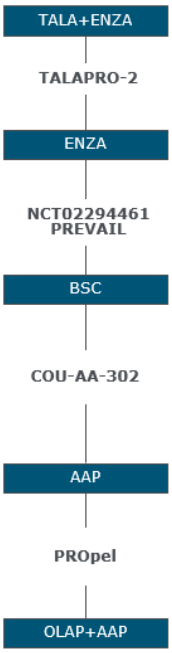
In sum, the NMA presented by the company in Document B suffered from substantial indirectness. It used four comparisons across five studies, to connect talazoparib with enzalutamide to olaparib with abiraterone (Figure 6). The NMA used a Cox model that relied on the assumption of proportional hazards (PH) across different covariates. The EAG's assessment, alongside assessment of PH in TA951,[18] was that the PH assumption was not met by the rPFS and OS efficacy data (HRs) from each of the studies in the network.

The EAG noted that violating the PH assumption can lead to biased estimates and inaccurate conclusions and requested the company replace their Cox proportional hazards model by using either an unanchored matching-adjusted indirect comparison (MAIC) based method or fractional polynomials.

An unanchored MAIC is a method for comparing treatments across trials where there is no common comparator (like a placebo arm) linking the trials. The EAG suggested a MAIC because it would address the indirectness (sparseness) present in the NMA. However, it would be unanchored and thus rely on modelling the absolute outcomes from the covariates, which would require the strong assumption that all relevant factors are accounted for.

A fractional polynomial (FP) network meta-analysis (NMA) is a method for analysing time-to-event data in NMA that uses fractional polynomials to model the hazard functions of interventions, allowing for flexible, non-proportional hazard modelling. The EAG suggested an FP NMA because it would address a key concern of the Cox NMA that the PH assumption was not met. While it would benefit from being an anchored approach, it would still suffer from the substantial indirectness (sparseness) of the network (Figure 6).

Figure 6: rPFS and OS network (N=5; reproduced from Figure 7, Doc B)



Abbreviations: AAP, abiraterone; BSC, best supportive care; ENZA, enzalutamide; OLAP+AAP, olaparib with abiraterone; OS, overall survival; rPFS, radiographic progression-free survival, TALA+ENZA, talazoparib with enzalutamide.

3.3.1. Proportional hazards NMA

The EAG will report the results of the PH NMA here as they will be referred to in comparison to the MAIC and FP NMA in later sections. The EAG preferred the fixed effect (FE) analysis and has reported those results. The EAG understood this analysis used the 16th August 2022 data cut from **TALAPRO-2**. The company presented "alternative sources of time-constant OS" and attributed these to the MAIC and PH NMA in Table 6 in the response to clarification question A6. However, it was unclear to the EAG what data cut these were from and they will not be further addressed in this report.

3.3.1.1. Input data for TALAPRO-2 and PROpel in the PH NMA

The Company reported input data for the studies included in the NMAs. The input data from **TALAPRO-2** and **PROpel** is detailed in Table 16.

Table 16: Input data for TALAPRO-2 and PROpel (adapted from Tables E.1 and E.2 in the Pfizer - Talazoparib Global NMA Final Technical Report, 2023)

Trial	Treatment	HR (95% CI)
Radiographic progression-free survival		
TALAPRO-2	Talazoparib with enzalutamide versus placebo with enzalutamide	0.63 (0.51,0.78)
PROpel	Olaparib with abiraterone versus placebo with abiraterone	0.67 (0.56,0.81)
Overall survival		
TALAPRO-2	Talazoparib with enzalutamide versus placebo with enzalutamide	0.89 (0.69,1.14)
PROpel	Olaparib with abiraterone versus placebo with abiraterone	0.83 (0.66,1.03)

3.3.1.2. Radiographic progression-free survival

The analysis found talazoparib with enzalutamide to have a [redacted] all the comparators. Olaparib with abiraterone and enzalutamide were [redacted] with abiraterone [redacted]. However, all active treatments had a [redacted] best supportive care (BSC).

Table 17: Summary of treatment effects vs talazoparib with enzalutamide for rPFS, comparison of NMA analyses (adapted from Table 7 in the cost comparison clarification response)

Active treatment	HR vs talazoparib with enzalutamide (95% CrI)
Best supportive care	[redacted]
Abiraterone acetate	[redacted]
Enzalutamide	[redacted]
Olaparib with abiraterone	[redacted]

The reference treatment for this table is TALA+ENZA. A HR>1 indicates inferiority to talazoparib with enzalutamide.
Abbreviations: CrI, Credible interval; HR, Hazard ratio; rPFS, radiographic progression-free survival.

3.3.1.3. Overall survival

The analysis found talazoparib with enzalutamide to have a [redacted] to olaparib with abiraterone and enzalutamide, a [redacted] abiraterone, and a [redacted] BSC.

Table 18: Summary of treatment effects vs talazoparib with enzalutamide for OS, comparison of NMA analyses (adapted from Table 8 in the cost comparison clarification response)

Active treatment	HR vs talazoparib with enzalutamide (95% CrI)
Best supportive care	[redacted]
Abiraterone acetate	[redacted]
Enzalutamide	[redacted]
Olaparib with abiraterone	[redacted]

The reference treatment for this table is TALA+ENZA. A HR>1 indicates inferiority to talazoparib with enzalutamide.
Abbreviations: CrI, Credible interval; HR, Hazard ratio; OS, overall survival.

3.3.2. Matching-adjusted indirect comparison

In response to the cost comparison EAR, the company presented an unanchored MAIC comparing talazoparib with enzalutamide to olaparib with abiraterone in Section 1.2 of the Addendum. MAICs aim to make two different study populations appear as if they were drawn from the same underlying population, thereby reducing bias when comparing treatments. The company selected participants from **TALAPRO-2**, for which the company has individual patient data (IPD), who matched the inclusion criteria of the comparator trial (**PROpel**). In addition, they reweighted participants in **TALAPRO-2** to make the populations more similar with respect to key baseline characteristics.

3.3.2.1. Feasibility of a MAIC

The MAIC was conducted in January 2025 and used the pivotal trials for the intervention and comparator which were **TALAPRO-2** (talazoparib with enzalutamide) and **PROpel** (olaparib with abiraterone). The EAG were not aware of any relevant trials of the two treatments that were not included in the analysis. However, the EAG were not able to undertake exhaustive searches in the time frame of the appraisal.

The company stated that a feasibility analysis was undertaken to determine the suitability of an unanchored MAIC to indirectly compare talazoparib with enzalutamide and olaparib with abiraterone. It was unclear exactly how this was approached by the company, but the factors they used were the presence of heterogeneity in terms of trial design characteristics, patient eligibility criteria, baseline patient characteristics, and outcome characteristics (i.e., definitions

and methods of reporting outcomes). The EAG have presented a feasibility analysis using those factors, and also subsequent treatments received, in the following sections.

Trial design characteristics and participant eligibility criteria

An overview of the methods used in the pivotal trial for talazoparib with enzalutamide (**TALAPRO-2**), and the pivotal trial for the comparator treatment, olaparib with abiraterone (**PROpel**), is provided in Table 19. Both were similarly sized, multicentre, Phase 3 trials, with over a hundred locations across the world. The EAG's clinical experts noted that the eligibility criteria were similar for each trial. Both trials recruited people with mCRPC with progressive disease and an ECOG performance status of 0 or 1. The two trials were alike in terms of exclusion criteria and concomitant medications that were, and were not, permitted. However, one notable difference in eligibility criteria, that the company highlighted in the addendum, was Pain Inventory - Short Form (BPI-SF). **TALAPRO-2** required patients to have a score ≤3 (no/mild pain) on question 3 of the BPI-SF (worst pain in the last 24 hours) while **PROpel** did not have any restrictions based on BPI-SF (0-10). Therefore, it was not possible to match the participants **TALAPRO-2** with the participants in **PROpel** for baseline pain because **PROpel** had notable broader inclusion criteria. For the same reason it was not possible to adjust the analysis baseline pain in the MAIC. The other differences between **TALAPRO-2** and **PROpel** in trial design characteristics and participant eligibility criteria were small and of no concern.

Table 19: Comparative summary of trial methodology

Study	TALAPRO-2: NCT03395197[22]	PROpel: NCT03732820[40]
Location	287 sites in 26 countries (including the UK)	132 sites in 17 countries (including the UK)
Trial design	Randomised, double-blind, placebo-controlled, Phase 3 study	Randomised, double-blind, placebo-controlled, Phase 3 study
Number of participants	N=805 (cohort 1[a])	N=796
Eligibility criteria	- Adults with mCRPC; - Progressive disease at study entry; - ECOG performance status ≤1; - Life expectancy ≥12 months as assessed by the investigator.	- Adults with mCRPC; - Progressive disease at study entry; - ECOG performance status ≤1; - Life expectancy ≥6 months as assessed by the investigator.
Exclusion criteria	Any prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state;	Prior cytotoxic chemotherapy, ARPis, or other systemic treatment in the mCRPC setting;

Study	TALAPRO-2: NCT03395197[22]	PROpel: NCT03732820[40]
Interventions evaluated	Talazoparib (0.5 mg/day) + enzalutamide (160mg/day) versus Placebo + enzalutamide (160mg/day)	Olaparib (600 mg/day) + abiraterone (1000mg/day) and prednisolone (10mg/day) versus Placebo + abiraterone (1000mg/day) with prednisone (10mg/day)
Concomitant medication	Prohibited: prednisone >10 mg , cytotoxic chemotherapy, hormonal therapy, other PARP inhibitor. Permitted: bisphosphonates or denosumab, ADT, hematopoietic growth factors, ESAs or RBC transfusions.	Prohibited: concurrent anticancer therapy, including investigational agents, while on study treatment. Permitted: bisphosphonates or denosumab for bone disease.
Primary outcomes	BICR-assessed rPFS or death	Investigator-assessed ibPFS or death
Key secondary outcomes	- Overall survival (OS) - Quality of life using EQ-5D-5L - Adverse events	- Overall survival (OS) - Quality of life using EQ-5D-5L - Adverse events

Abbreviations: ADT, androgen deprivation therapy; ARPis, androgen receptor pathway inhibitors; BICR, Blinded independent central review; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol five dimension (five level); ESA, erythropoietin stimulating agents; HRR, homologous recombination repair; ibPFS, imaging-base progression free survival; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PARP, Poly ADP ribose polymerases; PSA, prostate specific antigen; RBC, red blood cells; rPFS, radiographic progression-free survival.

Note(s): [a] Cohort 1 were recruited to the trial and were not selected based on their HRR status.

Baseline patient characteristics

While the baseline characteristics of the participants in each trial were similar, the EAG's clinical experts noted that the participants in the **PROpel** trial appeared to be slightly fitter (Table 20). This was demonstrated by a higher proportion of participants in **TALAPRO-2** who had prior treatment with androgen receptor pathway inhibitors / novel hormonal agents (ARPis/NHA), an ECOG performance status 1, and a high Gleason score (eight or higher). The MAIC adjusted for each of these factors. Also, as noted in the previous section, the trials differed in eligibility criteria for pain score (BPI-SF), and all the participants in **TALAPRO-2** had no pain or mild pain at study entry, compared to 71.2% in **PROpel**.

Table 20: Baseline characteristics of participants in TALAPRO-2 and PROpel

Characteristic	TALAPRO-2[22] Talazoparib with enzalutamide (n=402)	PROpel[40] Abiraterone and Olaparib (n=399)
Median age, years (range)	71 (66-76)	69.0 (43–91)

Characteristic	TALAPRO-2[22] Talazoparib with enzalutamide (n=402)	PROpel[40] Abiraterone and Olaparib (n=399)
Gleason score ≥8, n (%)	281 (70)	265 (66.4)
Median baseline serum PSA, µg/L (range/IQR)	18.2 (range: 6.9-59.4)	17.90 (IQR: 6.09–67.00)
BPI-SF ≤3, n (%)	402 (100)	284 (71.2)*
Disease site, n (%)		
Bone (including with soft tissue component)	349 (87)	349 (87.5)
Lymph node	147 (37)	215 (53.9) - Distant and locoregional
Visceral (lung)	45 (11)	40 (10.0)
Visceral (liver)	12 (3)	15 (3.8)
Other soft tissue	37 (9)	47 (11.8) - Prostate and adjacent structures
ECOG performance status, n (%)		
0 (normal activity)	259 (64)	286 (71.7)
1 (restricted activity)	143 (36)	112 (28.1)
Previous docetaxel treatment, n (%)	86 (21)	97 (24.3)
Prior treatment with NHA/ARPis	23 (6)	1 (0.3)
HRR gene alteration status by prospective tumour tissue testing, n (%)		
Deficient	85 (21)	111 (27.8)
Non-deficient	207 (51)	279 (69.9)
Unknown	110 (27)	9 (2.3)

* reported as 0 (no pain) – <4 (mild pain) in STA clarification response (A5)
Abbreviations: ARPi, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory (Short Form); ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; NHA, novel hormonal agents; PSA, prostate-specific antigen.

Definitions and methods of reporting outcomes

The outcomes assessed in the MAIC were rPFS and OS. In **TALAPRO-2** and **PROpel**, rPFS was assessed by blinded independent central review (BICR), and defined as time from randomisation to radiographic progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or death from any cause, whichever occurs first. In both trials, OS was defined as the time from randomisation to death from any cause. The EAG did not have concerns related to differences in the definitions or methods of reporting outcomes.

Subsequent therapies

At the clarification stage (A2), the company reported subsequent therapies received by participants in **TALAPRO-2** (median follow-up: [redacted] months) and **PROpel** (median follow-up: 19.4 months). The EAG have reported the subsequent treatments received in the two intervention arms in Table 21. In **TALAPRO-2**, 26.9% of people had taxane-based therapy / other cytotoxic chemotherapy, and in **PROpel**, 22.9% of people had cytotoxic chemotherapy. In **TALAPRO-2**,16.6% of people in had second generation androgen receptor inhibitors / androgen biosynthesis inhibitors, and in **PROpel**, 11.5% of people had hormonal therapy. While, it appeared to the EAG that similar proportions of people in each trial had cytotoxic chemotherapy or hormonal therapy, it was not possible to drawn firm conclusions from these data because the two trials used different categories to summarise the subsequent treatments, and the follow-up time was very different.

Table 21: Subsequent treatments in the intervention arms of TALAPRO-2 and PROpel (adapted from Tables 1 and 2, STA clarification response)

	TALAPRO-2: Talazoparib with Enzalutamide (N=398)		**PROpel: Olaparib with abiraterone (N=399)**
Median follow-up time	[redacted] months		19.4 months
Taxane-Based Therapy	[redacted]	Cytotoxic Chemotherapy	91 (22.9)
Second Generation Androgen Receptor Inhibitors	[redacted]	**Hormonal Therapy**	46 (11.5)
Radiopharmaceuticals	[redacted]	**Immunotherapy**	11 (2.8)
Single-agent PARP Inhibitor Therapies	[redacted]	**Targeted therapy**	6 (1.5)
Cellular Immunotherapy	[redacted]	**PARP inhibitor**	0
Androgen Biosynthesis Inhibitors	[redacted]	**Other**	3 (0.8)
Other Cytotoxic Chemotherapy	[redacted]		

* reported as 0 (no pain) – <4 (mild pain) in STA clarification response (A5)

Abbreviations: ARPi, androgen receptor pathway inhibitor; BPI-SF, Brief Pain Inventory (Short Form); ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; NHA, novel hormonal agents; PSA, prostate-specific antigen.

Conclusions on the feasibility of a MAIC analysis

The company concluded that while there was some inter-trial heterogeneity, these differences did not preclude using an unanchored MAIC analysis for rPFS and OS. Overall, the EAG agreed with company's feasibility assessment, though some concerns remained related to differences between the trials in baseline pain score (BPI-SF).

3.3.2.2. MAIC methodology

A MAIC can be anchored or unanchored. It can be anchored, where a common comparator arm, such as placebo, exists across the studies or unanchored where there is no common treatment arm. Therefore, anchored MAICs requires a weaker assumption than unanchored MAIC, as it focuses on relative effects rather than absolute outcomes. Unanchored MAIC assumes that all prognostic factors and effect modifiers are included in the analysis, which is a very strong assumption that is often difficult to meet. They do this by *balancing* the baseline characteristics (covariates) of the index and competitor trials to make them more similar and re-weighting individual patient data (IPD) from one trial to better reflect the characteristics of another trial's summary statistics. Balance is crucial in MAICs because it aims to minimise bias that can arise from differences in the patient populations or baseline characteristics between the trials being compared.

The company presented an unanchored MAIC and reported on the methodology in Section 1.2.1.2 of the addendum. As noted above, the company had to account for all factors that influence absolute outcomes, including both effect modifiers and prognostic variables. At the clarification stage (A4), the company presented visual and statistical tests of proportionality for the MAICs.

Prognostic variables and effect modifiers

The company identified 12 prognostic factors / treatment effect modifiers (Table 22Table 22). These were identified and ranked through a paper on the development and validation of a prognostic model for overall survival in chemotherapy-naive men with mCRPC,[41] and "refined" based on clinical expert opinion.

There were three factors in the 12 ranked that could not be adjusted for: time to mCRPC from continuous ADT, BPI-SF, and neutrophil to lymphocyte ratio. The EAG's clinical experts stated that it was not ideal that the MAICs could not adjust for the top ranked factor (time to mCRPC).

They did note that given both trials were recruiting people in similar settings with similar prior therapies, it was not unreasonable to assume that they were similar in terms of time to CRPC. Also, time to CRPC was likely to be non-independent from other factors (presence of liver metastases, number of bone metastases, and Gleason score, particularly) so time to CRPC was partly corrected through adjustment for those. The EAG's experts were less concerned that it was not possible to adjust for neutrophil to lymphocyte ratio. They considered it likely that neutrophil to lymphocyte ratio was reasonably balanced across the two trials.

As explained in Section 3.3.2.1, eligibility criteria for **TALAPRO-2** were restricted recruitment to people with no or mild pain (BPI-SF ≤3). However, **PROpel** had not such restriction and 28.8% of participants had moderate, severe, or unknown pain at baseline. Therefore, it was not possible to either match the participants in **TALAPRO-2** to **PROpel**, or to adjust the analysis for baseline pain. A clinical expert advised the EAG that pain is a prognostic modifier for people with mCRPC and it would have been better if the populations could have been matched for pain. The EAG noted that this meant the participants in were **PROpel** harder to treat and, as such, this favoured talazoparib and enzalutamide. It was unclear to the EAG whether this resulted in any meaningful benefits for talazoparib and enzalutamide versus olaparib abiraterone but the EAG maintain that it contributed to further uncertainty around the MAIC.

The company also considered the factors by which participants in **TALAPRO-2** were stratified at randomisation. These were HRR alteration status, prior ARPis/NHT and taxane-based therapy in the castration-sensitive prostate cancer (CSPC) stage. The EAG's clinical experts stated that it was important to adjust for HRR status and prior therapy at the CSPC stage.

The company did not use the MAIC adjusted for exploratory factors (BRCA1/2) in their cost-effectiveness analysis. However, the EAG was not concerned because the MAIC was adjusted for HRR status, and that included BRCA1, BRCA 2, and PALB2.

The EAG's experts did not note any further factors for which adjustment was crucial for the MAIC. However, they mentioned that the company could have considered adjusting for age alongside the other factors.

Table 22: Adjustment of prognostic factors for PROpel (adapted from Tables 3 and 4, CS Addendum)

Rank	Identified Factor	Available for TALAPRO-2	Available for PROpel	Adjusted variable
1	Time to mCRPC from continuous ADT	No [a]	No [a]	No
2	Presence of liver metastases	Yes	Yes	Yes
3	Number of bone metastases (<10 vs >10)	Yes [b]	Yes [b]	Yes
4	ECOG (0-1 vs 2, 3)	Yes [c]	Yes [c]	Yes
5	BPI-SF	Yes	Yes	No
6	PSA kinetics or PSA levels in absence of kinetics data	Yes	Yes	Yes
7	Gleason score	Yes	Yes	Yes
8	Haemoglobin level	Yes	Yes	Yes
9	Lactate dehydrogenase level	Yes	Yes	Yes
10	Albumin level	Yes	Yes	Yes
11	Alkaline phosphatase level	Yes	Yes	Yes
12	Neutrophil to lymphocyte ratio	Yes [d]	No	No
Strat factor	HRR alt. status	Yes	Yes	Yes
Strat factor	Prior NHT	Yes	Yes	Yes
Strat factor	Prior Taxane-based therapy	Yes	Yes	Yes
Exploratory*	BRCA1	Yes	Yes	Yes
Exploratory*	BRCA2	Yes	Yes	Yes
Exploratory*	PALB2	Yes	No	No

[a] Trial reported median time from initial diagnosis to randomisation date.
[b] Trial reported presence/absence of bone metastases.
[c] All participants had ECOG 0 or 1.
[d] Calculated from number of neutrophils and lymphocytes.
Abbreviations: ADT, androgen deprivation therapy; alt, alteration; BPI-SF, Brief Pain Index - Short Form; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHT, novel hormonal therapy; PSA, prostate-specific antigen; strat, stratification.

3.3.2.3. Proportionality

Ensuring proportionality is crucial for the validity of MAIC analyses, as it helps to avoid bias and ensure that the results are not unduly influenced by the specific choice of weights. At the clarification stage (A4), the company presented visual and statistical tests of proportionality for the MAIC (Grambsch-Therneau test, plots of Schoenfeld residuals, and log-log plots).

rPFS

The plot of Schoenfeld residuals for rPFS did not indicate a violation of the proportional hazards assumption. Similarly, while the log-log plots were not quite parallel they indicated rPFS was adequately described by the adjustment for prognostic factors. The company also presented a Grambsch-Therneau test for the proportional hazards assumption and it was non-significant (p-value = 0.1865 for rPFS), indicating a hazard ratio is not an inappropriate measure of summary of effect.

OS

The plot of Schoenfeld residuals for OS did not indicate a violation of the proportional hazards assumption. Similarly, while the log-log plots were not quite parallel they indicated OS was adequately described by the adjustment for prognostic factors. The company also presented a Grambsch-Therneau test for the proportional hazards assumption and it was non-significant (p-value = 0.1049 for OS), indicating a hazard ratio is not an inappropriate measure of summary of effect.

3.3.2.4. MAIC performance assessment and scenario analysis

The company presented the distribution of baseline characteristics before and after the adjusting process (Table 23). There were 402 participants in **TALAPRO-2** in the naïve analysis, and after matching and adjustment for the nine primary factors and three stratification factors, the effective sample size (ESS) was [redacted] ([redacted]%; [redacted]% reduction). The company stated that an ESS of >43% of the original sample size is occasionally cited as a NICE guideline for sufficient ESS and referenced the NICE DSU Technical Support Document (TSD) 18.[42] The EAG could not find any reference to “sufficient” ESS in the cited report. However, the TSD noted that the three papers reviewed that reported ESS, saw an 80% average reduction from the original sample size (range: 57–98%). The reduction in this case was substantially lower than that, and while some reduction is expected due to weighting, a small reduction suggested that the studies were not significantly different, and the MAIC may be less prone to bias.

The company did report scenario analyses were conducted to investigate the impact on the treatment effect estimates, ESS, and SMD when adjusting for additional covariates in the analyses. The analyses were conducted sequentially, adjusting incrementally for the remaining factors in order of importance, until the final model contained all available factors.

Table 23: Unadjusted and adjusted baseline characteristics (reproduced from Table 4, CS Addendum)

Characteristics	PROpel	TALAPRO-2														
		Naïve	1 Strat Factor	2 Strat Factors	3 Strat Factors	1 Factor	2 Factors	3 Factors	4 Factors	5 Factors	6 Factors	7 Factors	8 Factors	9 Factors (Primary)	10 Factors (Exploratory)	11 Factors (Exploratory)
HRR alt. status (%)	27.8 %	[redacted]	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%	27.8%
Prior NHT (%)	0.3%	[redacted]	[redacted]	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
Prior Taxane (%)	24.3 %	[redacted]	[redacted]	[redacted]	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%	24.3%
Liver metastases (%)	3.8%	[redacted]	[redacted]	[redacted]	[redacted]	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%	3.8%
Bone metastases (%)	87.5 %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%	87.5%
ECOG = 1 (%)	28.1 %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%	28.1%
PSA [a] > 17.9 µg/L (%)	50.0 %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%	50.0%
Gleason score ≥ 8 (%)	66.4 %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66.4%	66.4%	66.4%	66.4%	66.4%	66.4%	66.4%
HGB [b] (mean [SD])	130.5 (12.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)	130.5 (12.8)
LDH [b,c] (mean [SD])	3.9 (1.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.9 (1.3)	3.9 (1.3)	3.9 (1.3)	3.9 (1.3)	3.9 (1.3)
Albuminb (mean [SD])	42.4 (3.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42.4 (3.9)	42.4 (3.9)	42.4 (3.9)	42.4 (3.9)
ALP [b] (mean [SD])	2.6 (2.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.6 (2.1)	2.6 (2.1)	2.6 (2.1)
BRCA1 (%)	2.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2.3%	2.3%
BRCA2 (%)	9.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	9.5%

Characteristics	PROpel	TALAPRO-2														
		Naïve	1 Strat Factor	2 Strat Factors	3 Strat Factors	1 Factor	2 Factors	3 Factors	4 Factors	5 Factors	6 Factors	7 Factors	8 Factors	9 Factors (Primary)	10 Factors (Exploratory)	11 Factors (Exploratory)
N or ESS	*N = 399*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*ESS = 291*
Mean SMD		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*0.000*

[a] PSA level was converted to a dichotomous variable and used the median PSA level from PROpel as the cut-off (17.9 µg/L). To achieve half of the population with PSA levels below the median and half with PSA levels above median, the sample size of PROpel was set to 398 patients for this variable. Grey shading denotes when the value for that characteristic (i.e., row) has been adjusted from the PROpel value.
[b] The mean and standard deviation were estimated from the reported median and range using the estmeansd package in R.
[c] PROpel reported in µkat/L whereas TALAPRO-2 used U/L. A conversion of 1 µkat/L = 60 U/L was performed to match the unit used in PROpel
Abbreviations: ALP, alkaline phosphatase level; BPI-SF, Brief Pain Inventory - Short Form; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ESS ,effective sample size; HGB ,haemoglobin level; HRR, homologous recombination repair; LDH, lactate dehydrogenase level; MAIC, matching-adjusted indirect comparison; NHT, novel hormonal therapy; PSA, prostate specific antigen; SD, standard deviation; SMD, standardised mean difference.

3.3.2.5. MAIC results

The company presented the results in Section 1.2.1.3 of the addendum. The results reported by the company were those after adjustment for the three stratification factors and the nine primary factors. The company did report the results after the additional adjustment for the exploratory factors (BRCA1/BRCA2). However, the EAG also noted that HRR status was a stratification factor and includes BRCA1 and BRCA2 alterations, so a second adjustment for those factors was not appropriate.

Radiographic progression-free survival

The primary MAIC analysis (adjusted for primary factors and stratification factors) found talazoparib with enzalutamide had a [redacted] olaparib with abiraterone in rPFS (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]). Exploratory analyses adjusting for BRCA gene alterations also demonstrated [redacted] result to the primary analysis. The company presented a weighted Kaplan-Meier (KM) curve for the primary analysis (all primary factors and stratification factors adjusted for) and this has been reproduced in Figure 7.

Figure 7: Weighted rPFS KM for TALAPRO-2 vs PROpel (primary analysis; reproduced from Figure 4 in the Addendum)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OLAP+AAP, olaparib with abiraterone acetate; rPFS, radiographic progression-free survival; TALA+ENZA, talazoparib with enzalutamide.

Overall survival

The primary MAIC analysis (adjusted for primary factors and stratification factors) found talazoparib with enzalutamide had a [redacted] olaparib with abiraterone for OS (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]). The company presented a weighted Kaplan-Meier (KM) curve for the primary analysis (all factors adjusted for) and this has been reproduced in Figure 8.

Figure 8: Weighted OS KM for TALAPRO-2 vs PROpel (primary analysis; reproduced from Figure 6, Addendum)

[redacted]

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OLAP+AAP, olaparib with abiraterone acetate; rPFS, radiographic progression-free survival; TALA+ENZA, talazoparib with enzalutamide.

3.3.2.6. Conclusions on the MAIC

The MAIC demonstrated that talazoparib with enzalutamide had a [redacted] olaparib with abiraterone for rPFS and a [redacted] olaparib with abiraterone for OS.

The MAIC addressed concerns related to the PH NMA conducted by the company. It addressed the indirectness of the NMAs and the visual and statistical tests of proportionality presented at

clarification did not raise any further concerns related to the proportionality of either the rPFS or OS MAICs. However, the EAG was concerned the trials could not be matched or adjust for pain at baseline and pain is prognostic modifier for people with mCRPC. The EAG noted that this meant the participants in were **PROpel** harder to treat and, as such, this favoured talazoparib and enzalutamide. It was unclear to the EAG whether this resulted in any meaningful benefits for talazoparib and enzalutamide versus olaparib abiraterone but the EAG maintained that it contributed to uncertainty around the MAIC. Also, the MAIC did not adjust for the top ranked factor (time to mCRPC) but had clinical advice that, while this was a valid concern and risk of bias, it did not invalidate the analysis.

In sum, the EAG did not consider the results of the unanchored MAIC to be robust and were subject to substantial uncertainty. However, they did not suffer from the lack of proportionality and indirectness present in the PH NMA, and as such, were appropriate for use in the company's cost utility analysis.

3.4. Additional work on clinical effectiveness undertaken by the EAG

The EAG did additional work linked to the safety of talazoparib with enzalutamide and the safety of olaparib with abiraterone. The EAG also critiqued the FP NMA that was presented nine days prior to the submission on this report.

3.4.1. Safety of talazoparib with enzalutamide and olaparib with abiraterone

In this section, the EAG compared the safety reported in the talazoparib with enzalutamide arm in **TALAPRO-2** with the olaparib with abiraterone arm in **PROpel**.

3.4.1.1. Drug dosing exposure

The drug exposure of the intervention arms reported in **TALAPRO-2** and in **PROpel** are presented below in Table 24. No TTD was reported but the median time on treatment with talazoparib ([redacted] weeks) or olaparib (~79 weeks) were similar between the treatment arms. There were higher rates of dose interruptions, dose reductions, and drug discontinuations, due to adverse events, for talazoparib than olaparib. In addition, a higher proportion of people on enzalutamide than abiraterone had dose interruptions, dose reductions, and drug discontinuations. However, the EAG caution that there were differences in the eligibility criteria in each trial and this was a naïve comparison.

Table 24: Summary of the drug dosing exposure for the intervention arms in the TALAPRO-2 and PROpel trials

	Talazoparib with enzalutamide (n=398)[43]	Olaparib with abiraterone (n=398)[44]
Duration of treatment with talazoparib/olaparib		
N	397	397
Mean (SD)	79.8 (46.9) weeks	NR
Median (range)	86.0 (0.29, 186.1) weeks	17.5 months or ~76 weeks
Dose interruptions talazoparib/olaparib, n (%)	268 (67.3)	NR
Due to AE	235 (59.0)	178 (44.7)
Due to other reasons	110 (27.6)	NR
Dose interruptions due to AE enzalutamide/abiraterone, n (%)	156 (39.1)	131 (32.9)
Dose reductions talazoparib/ olaparib, n (%)	218 (54.8)	NR
Due to AE	209 (52.5)	80 (20.1)
Due to other reasons	13 (3.3)	NR
Dose reductions due to AE enzalutamide/abiraterone, n (%)	58 (14.6)	10 (2.5)
AE resulting in permanent drug discontinuation of:		
Talazoparib/olaparib, n (%)	75 (18.8)	55 (13.8)
Enzalutamide/abiraterone, n (%)	43 (10.8)	34 (8.5)

Abbreviations: AE, Adverse event; NR, not reported; SD, Standard deviation.

3.4.1.2. Adverse events

A summary of adverse events (AEs) in the talazoparib with enzalutamide arm of **TALAPRO-2** and the olaparib with abiraterone arm of **PROpel** is presented below in Table 25. There was a substantially higher rate of Grade ≥3 adverse events in the talazoparib with enzalutamide arm (299, 75.1%) compared to the olaparib with abiraterone arm (188, 47.2%). There was also a higher rate of serious AEs (39% versus 33.9%) and a higher proportion of Grade ≥3 anemia, fatigue, back pain, and hypertension events in the talazoparib with enzalutamide arm than the olaparib with abiraterone arm. As previously noted, there were differences in the eligibility criteria in each trial and this was a naïve comparison. However, despite the differences in populations recruited, the EAG considered this to be evidence that talazoparib with enzalutamide had a higher drug toxicity than olaparib with abiraterone.

Table 25: Summary of adverse events occurring in the intervention arms in the TALAPRO-2 and PROpel trials

	Talazoparib with enzalutamide (n=398)[43]		Olaparib with abiraterone (n=398)[44]	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE, n (%)	392 (98.4)	299 (75.1)	387 (97.2)	188 (47.2)
Treatment-related AE, n (%)	357 (90.0)	234 (58.8)	NR	NR
Serious AE, n (%)	157 (39.4)	145 (36.4)	135 (33.9)	NR
Serious and treatment-related AE, n (%)	78 (20.0)	68 (17.1)	NR	NR
Grade 5 AE, n (%)	13 (3.3)	-	NR	NR
Common AEs (all AEs in ≥10% of total participants), n (%)				
Anaemia	262 (65.8)	185 (46.5)	183 (46.0)	60 (15.1)
Neutropenia	142 (35.7)	73 (18.3)	NR	NR
Fatigue	134 (33.7)	16 (4.0)	148 (37.2)	9 (2.3)
Thrombocytopenia	98 (24.6)	29 (7.3)	NR	NR
Back pain	88 (22.1)	10 (2.5)	68 (17.1)	3 (0.8)
Leukopenia	88 (22.1)	25 (6.3)	NR	NR
Decreased appetite	86 (21.7)	5 (1.3)	58 (14.6)	4 (1.0)
Hypertension	55 (13.8)	21 (5.3)	50 (12.6)	14 (3.5)
Venous embolic and thrombotic events	NR	NR	29 (7.3)	27 (6.8)

Abbreviations: AE, adverse events; NR, not reported.

3.4.2. Fractional polynomials

At the clarification stage, the company requested a timeline extension from NICE to deliver an ITC using a FP approach. The FP NMA provided appeared to be conducted to a good standard, though timelines for the delivery of additional data precluded replication of analyses. In their report of the FP NMA, the company highlighted that non-convergence impacted all OS analyses, a result that was not unexpected given the high levels of indirectness present in the analysis, and identified a small number of single-power polynomials demonstrating favourable properties for rPFS. The company noted that a criterion for rejection of polynomial fits was wide credible intervals. The EAG did not regard this at face as a relevant criterion, as the indirectness of the analysis would be expected to generate such a result, but this did not impact the company's or EAG's conclusion.

Of the relevant fits for rPFS, several were taken forward for further analysis on the basis of visual fit and low deviance information criterion (DIC). The fit that had the lowest DIC (p = -1), and the EAG questioned the extent of the validation undertaken with respect to other sources to complement this criterion in selecting an optimal fit. As highlighted in Section 4.2.6, the absence of a complementary FP NMA estimate for OS meant that subsequent cost-effectiveness modelling required a blending of estimates from MAIC and FP NMA analyses. The EAG regarded this as not ideal, given it could not trace the provenance of some of the OS relative effect estimates cited. In consideration of the foregoing reasons, the EAG does not consider effectiveness estimates from the FP NMA further.

3.4.3. Comparison of the results of the ITCs

The company presented three ITCs in the CS. Each were subject to substantial limitations as summarised in Key Issue 2. As noted, the EAG considered the unanchored MAIC to be the most appropriate ITC presented, however, it would also be useful to compare the results of each.

3.4.3.1. Radiographic progression-free survival

The PH NMA (fixed effect) for rPFS, presented in Document B, found talazoparib with enzalutamide to have a [redacted] over olaparib with abiraterone: HR [redacted]; 95% CrI [redacted]. The EAG's preferred ITC was the MAIC, and also resulted in a statistically significant benefit, but the benefit was smaller: HR [redacted]; 95% CI [redacted]. The FP NMA produced time-varying rPFS HR using first-order FP model with p=-1. The effect of the time-varying rPFS HR on the cost-effectiveness estimates can be seen in scenario analyses presented in Section 5.2.3 (company scenario analysis) and 6.4 (scenario analysis on top of the EAG base case). The company presented plots of the time-varying HRs for this solution, and two other 1st order models, in Figure 7 (CQ A6). In the company's chosen solution, the HR olaparib with abiraterone over talazoparib with enzalutamide[redacted] after about 18 months. Other solutions offered [redacted], with [redacted] demonstrating continued reduction of the HR over the time horizon.

3.4.3.2. Overall survival

The PH NMA (fixed effect) for OS, presented in Document B, found talazoparib with enzalutamide to have a [redacted] to olaparib with abiraterone: HR [redacted]; 95% CrI [redacted]. The EAG's preferred ITC was the MAIC and found a [redacted] for talazoparib with

enzalutamide: HR [redacted]; 95% CI [redacted]. Results from the FP NMA were not available for this outcome.

3.5. Conclusions of the clinical effectiveness section

Based on the above evidence the EAG considered talazoparib with enzalutamide to be an effective treatment for people with mCRPC. The pivotal trial, **TALAPRO-2**, demonstrated it offered a [redacted] over placebo with enzalutamide for rPFS and OS. However, it also had a higher AE burden than placebo with enzalutamide.

The population in the final scope issued by NICE were adults with mCRPC for whom chemotherapy is not clinically indicated. However, for reasons detailed in Section 2.3, current service provision is no longer contingent on whether chemotherapy is indicated. Clinicians are now likely to offer ARPi based treatment to people who are eligible for chemotherapy in the first line mCRPC setting. Therefore, the relevant population for this appraisal were people with mCRPC who cannot have, or do not want, chemotherapy. The evidence presented in the CS was appropriate for this adjusted population.

A further change from the final scope issued by NICE were the comparators (**Key Issue 1**). The final scope issued by NICE was published when this was a cost comparison appraisal and for reasons linked to a cost comparison approach, two relevant comparators at the same place in the treatment pathway were not included (enzalutamide / abiraterone with prednisone/prednisolone). At the clarification stage, the EAG requested that the company include these comparators, primarily enzalutamide as it has the largest market share and has been directly compared to talazoparib with enzalutamide in **TALAPRO-2**, in the cost effectiveness analysis.

Across the appraisal, the company submitted three ITCs. As detailed in **Key Issue 2**, the EAG considered there to be uncertainty linked to each estimate but the most appropriate was the unanchored MAIC. An unanchored MAIC assumes that all effect modifiers and prognostic factors are accounted for, and this assumption is largely considered impossible to meet. For example, the participants in the MAIC could not be matched, or the analysis adjusted, for baseline pain. This likely favoured talazoparib with enzalutamide, but it was unclear to what extent. The EAG still favoured the MAICs over the PH NMAs and FP NMAs but were aware of the substantial uncertainty linked to the results.

The MAIC found talazoparib with enzalutamide had a [redacted] olaparib with abiraterone for rPFS and OS. The benefit was [redacted] for rPFS and [redacted] for OS. There was also evidence from a naïve comparison of safety outcomes in the trial that talazoparib with enzalutamide had a higher drug toxicity than olaparib with abiraterone.

No MAIC was presented for abiraterone (with prednisone/prednisolone) but abiraterone was evaluated in the PH NMA. While the PH NMA was flawed, it was the only comparison of talazoparib with enzalutamide with abiraterone in the CS. The PH NMA for rPFS (Section 3.3.1.2) found abiraterone to be [redacted] than the active comparators but to have a [redacted] over BSC. The PH NMA for OS (Section 3.3.1.3) found it to be [redacted] to talazoparib with enzalutamide and olaparib with abiraterone, [redacted] to enzalutamide, and had a [redacted] over BSC.

The EAG's experts noted that talazoparib and olaparib are both PARP inhibitors and PARP inhibitors are understood to be more effective in cancer cells that have HRR deficiency. Olaparib with abiraterone was only offered to people with HRR deficient tumours in their practices and they expected to do the same with talazoparib and enzalutamide if a positive recommendation were made (**Key Issue 5**). The company appeared to be aware of this and noted research on a proposed synergistic effect between ARPis and PARP inhibitors (Sections 2.3.4). However, the EAG did not find adequate evidence had been presented to substantiate the proposed synergistic effect between PARP inhibition and ARPis (Section 3.2.3.2).

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company did not provide an update to the searches for health-related quality-of-life studies and healthcare resource use and economic evaluations which were conducted in October 2022. The EAG conducted their own update to the company's utilities searches, in order to identify publications after 3 October 2022, in Medline and Embase (both in Ovid); these searches identified 229 new references to screen after deduplication in EndNote (version 20). Seven[45-51] references were considered as relevant by the EAG, in particular the Castro 2024 paper,[51] which was used to inform the EAG model.

At the clarification stage, the company presented some update searches conducted in November 2024.These searches were well constructed and executed but did not pick up the same references as the EAG search due to the search date; in particular the Castro 2024[51] paper was not identified.

4.2. Summary and critique of company's submitted economic evaluation by the EAG

The EAG critique focusses on the economic model submitted by the company at clarifications stage. A number of assumptions were updated, additional data for TTD and RDI and 3 model corrections were made by the company at this stage (see Section B of CQ response).

4.2.1. NICE reference case checklist

Table 26: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Direct health effects for patients only which is appropriate for this condition
Perspective on costs	NHS and PSS	In line with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis without fully incremental analysis as enzalutamide, abiraterone with prednisolone and docetaxel which were all in the NICE scope related to this topic as an STA were not included in the original model supplied. The

Attribute	Reference case	EAG comment on company's submission
		lack of inclusion of enzalutamide was considered most problematic and the company supplied a separate model file for comparison to enzalutamide which used unweighted analysis and removed the comparison to olaparib with abiraterone thus not allowing for fully incremental analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	30 years, at which point less than [redacted] of patients remained alive in all arms in both models.
Synthesis of evidence on health effects	Based on systematic review	Based on systematic review, however, additional relevant data was supplied by NICE from TA951 and identified in update searches conducted by the EAG
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D-5L mapped to 3L from TALAPRO-2 for the rPFS state, TA377 for post-progression and palliative care. TA377 uses data from two published literature sources Wolff 2012[52] and Diels 2014[53] for post progression one of which uses FACT-P mapped to EQ-5D and the other EQ-5D data and Sandblom 2004 for palliative care which uses the EQ-5D. The sources used are not entirely in line with the NICE reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Broadly in line with reference case, tariff used in Wolff 2012 and Sandblom 2004 unclear
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Broadly in line with reference case, the updated source used for palliative care may include some non-reference case social care costs but excludes

Attribute	Reference case	EAG comment on company's submission
		reference case costs for palliative radiotherapy
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company used a partitioned survival analysis (PartSA). This assumed independence in the transitions to radiographic progression and death. This choice was not jusified in the CS. As noted in TSD19: "It is important to recognise that PartSA may not provide the ideal modelling approach to inform extrapolation due to the lack of structural relationship between modelled endpoints." In this case, however, OS was relatively mature with [redacted] events observed for talazoparib with enzalutamide and [redacted] for placebo with enzalutamide therefore within the remit of a pragmatic appraisal the EAG considered the choice reasonable. The EAG did, however, note that the survival curves originally chosen by the company led to a kink in the extrapolated rPFS curve where the functional forms chosen by the company lead to the curves crossing (see Figure 8 CS). This indicated issues with the chosen extrapolations; issues which are more likely to occur in a PartSA structure where independence between endpoints is assumed.

The progression state was delineated by receipt of subsequent treatment or palliative care. Only one round of treatment post progression was included. This was considered broadly reasonable in this clinical context.

4.2.3. Population

The population evaluated was adult patients with mCRPC for whom chemotherapy was not clinically indicated. This was in line with **TALAPRO-2** Cohort 1 and marketing authorisation.

The model comparing to olaparib with abiraterone used the unanchored MAIC to extrapolate survival for talazoparib with enzalutamide and olaparib with abiraterone which means that the population the model predicts for is the population in **PROpel**. The population characteristics used in the model for age and sex are from **TALAPRO-2** which is a minor inconsistency. The EAG noted the age profile of participants was similar (median 69 / 70 in the two arms in **PROpel** vs 71 in **TALAPRO-2**).

A separate model was submitted in response to clarification questions which compared to enzalutamide and predicts for the population included in **TALAPRO-2**. This was not ideal as it meant that the two comparisons were provided in somewhat different populations. This is addressed further in later sections.

The EAG also noted that the company did not supply cost-effectiveness analysis according to HRR subgroup as requested in the NICE scope. Clinical effectiveness results indicated that in comparison to enzalutamide greater effectiveness may be expected in HRR deficient patients with treatment compared to the HRR non-deficient or unknown subgroup (see Section 3.2.3.2). The direction of impact on cost-effectiveness results was less clear as greater effectiveness may be accompanied by a greater time on treatment. This increased uncertainty in the comparison to enzalutamide as clinicians indicated they predominantly use both PARP inhibitors in HRR deficient patients; a subgroup for which results were not presented.

4.2.4. Interventions and comparators

The intervention was talazoparib with enzalutamide. Two comparisons were provided by the company in their economic evaluation:

- Olaparib with abiraterone: provided initially
- Enzalutamide (within trial comparison): provided in response to CQ B2

The inclusion of both comparators was closer to the draft scope[2] issued for the STA version of this appraisal which also includes comparison to abiraterone with prednisone or prednisolone (see Section 2.4.2). It was also consistent with clinical advice to the EAG that there is no distinct population eligible for olaparib with abiraterone but not for the other treatments included in the scope. As a result, a recommendation for people in whom olaparib with abiraterone "would otherwise be offered" is clinically invalid. Finally, the inclusion of enzalutamide offered a valuable point of triangulation, particularly given concerns about the robustness of the presented ITCs.

Comparison to abiraterone was not provided by the company and was instead implemented by the EAG assuming equal effectiveness to enzalutamide in line with TA951.

The EAG noted that the NICE manual 2022[54] specifies that fully incremental analysis should be presented against (as opposed to pairwise comparisons) when the technology is not expected to specifically displace individual comparators. Clinical advice to the EAG was that there was no

clinical rationale for the selection of only olaparib with abiraterone as a comparator as all of the treatments in the scope were given to broadly the same patient population.

Fully incremental analysis was not presented by the company as they conducted the two comparisons in distinct Excel models stripping out the comparison to olaparib with abiraterone before adding the enzalutamide comparison. This was not ideal and not in line with the EAG's request at the clarification stage, which requested the addition of the enzalutamide arm to the existing Excel file. Additionally, comparison was presented in different populations (weighted MAIC population for olaparib with abiraterone and unweighted population for enzalutamide).

4.2.5. Perspective, time horizon and discounting

The economic analysis takes an NHS and PSS perspective and used a 3.5% discount rate for costs and QALYs in line with the NICE reference case. The model used a 30 year time horizon which was considered appropriate.

4.2.6. Treatment effectiveness and extrapolation

The company generated MAIC-weighted survivor-time data which was used to conduct extrapolation in the comparison to olaparib with abiraterone. Unweighted extrapolations were used in the comparison to enzalutamide.

Independent and dependent models were fitted to talazoparib with enzalutamide and olaparib with abiraterone, using the following distributions: log-normal, log-logistic, gamma, generalised gamma, Weibull, exponential, and Gompertz. The curve selection process for rPFS and OS involved an assessment of (1) statistical fit via Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), (2) visual fit (survivor function only), (3) comparison to the median survival estimates from **TALAPRO-2**, (4) clinical plausibility of long-term survival estimates based on the consultation with six UK clinical experts conducted during TA951 (olaparib with abiraterone in the same indication as this appraisal), and, (5) external validation/assessment against TA951.

The EAG also noted that by default this assumed that the treatment effect would continue for a patient's lifetime, no exploration of the uncertainty around this was conducted by the company.

The company took the starting point that the generalised gamma curve should be used for both rPFS and OS as this was what was done in TA951. The EAG fundamentally disagreed with this logic. Whilst using clinical input gained in TA951 was sensible and following the same rationale

for curve selection based upon NICE support documents made sense picking the same functional form by default does not as new data is available now that was not in TA951 and the generalised gamma curve in particular (with 3 parameters) was highly sensitive to the data input meaning that the resulting predictions could be considerably different.

In response to clarification questions where the EAG identified that the company's original curve selection led to the OS and rPFS curves crossing relatively early on in the model time horizon the company updated their curve selection to the log-normal curve for rPFS and the generalised gamma curve for OS in the comparison to olaparib with abiraterone (CQ B4). This was on the basis of clinical expert input from TA951 advising that the generalised gamma was the most appropriate curve for OS in that appraisal, advice sought from three clinicians by the company which advised that more pessimistic median rPFS estimates would be more appropriate for use and statistical fit. Scenario analysis was provided using the log-logistic curve for rPFS.

For TTD the company simply used the best statistical fit according to the lowest sum AIC/BIC for the respective arms.

In response to clarification question A6 the company submitted an economic analysis which used a fractional polynomial model for rPFS (p = -1) and a constant hazard ratio for OS due to lack of convergence of the FP NMA models (and constant hazard ratios for OS due to lack of convergence of the FP NMA models ([redacted] for olaparib with abiraterone over talazoparib with enzalutamide as preferred option based on MAIC using the final data cutoff 3rd September 2024; [redacted] as other options based on fixed-effects and random-effects NMA, respectively, using the final data cutoff 3rd September 2024). The EAG did not consider this a robust scenario analysis due primarily to the use of hazard ratios for OS being derived from analysis which was not provided to the EAG. The EAG note that OS, rather than rPFS, is the key model driver. We instead provide scenario analysis around the EAG base case to demonstrate the impact of use of the most and least optimistic FP NMA model whilst retaining the current source of information for OS.

4.2.6.1. OS

Extrapolated OS curves were adjusted for general population mortality informed by life tables for the UK to ensure the disease-related risk of death does not exceed general population estimates.

For both treatment arms in the MAIC weighted dataset, this transition occurred around [redacted], after which general population mortality was assumed to dominate. In the unweighted dataset this occurred at [redacted] in the OLA+ABI arm and at [redacted] in the TALA+ENZA arm. For the ENZA monotherapy vs TALA+ENZA, the model assumes general population mortality dominates at [redacted] in the ENZA monotherapy arm and at [redacted] in the TALA+ ENZA arm.

Olaparib with abiraterone – MAIC weighted population

All curves [redacted] at 12, 24, and 36 months, with a range of approximately [redacted] at 12 months [redacted] at 24 and 36 months. [redacted] was seen at 120 months with landmark survival estimates of [redacted] The mean AUC varies between [redacted] months (Gompertz) and [redacted] months (lognormal and generalised gamma).

The lognormal, log-logistic and generalised gamma curves had similarly good statistical fit and relatively similar long-term survival estimates (120-month survival [redacted] This was [redacted] the preferred curve selection from TA951 (generalised gamma: 17.1%).

The EAG agreed with the choice of the generalised gamma for the base case given alignment with prior clinical expert input within TA951. The EAG's experts stated that survival in **PROpel** and **TALAPRO-2**, on which assumptions are based in this model, was somewhat optimistic compared to the real-world due to both the usual factors in that the population treated in practice will be broader than enrolled in the trial and at the time of writing ARPis are now available in mHSPC meaning that those reaching mCRPC without having tried these therapies will be older and likely have more indolent disease. The landmark survival estimates predicted by the economic model were at the upper end of what the EAG's clinical expert considered clinically plausible.

Talazoparib with enzalutamide – MAIC weighted population

In terms of landmark estimates, all curves [redacted] at 12 months, 24 months, 36 months, 48 months, and 60 months, with a [redacted] between the most conservative and optimistic curves at 60 months although estimates [redacted] at 120 months ([redacted] landmark survival). The mean AUC varied between [redacted] months (Gompertz) and [redacted] months (generalised gamma).

Similar to olaparib with abiraterone the lognormal, log-logistic and generalised gamma curves had similarly good statistical fit and [redacted] long-term survival estimates (120-month survival [redacted]

Talazoparib with enzalutamide – unweighted population

All curves [redacted] at 12, 24, and 36 months. [redacted] was seen at 120 months with landmark survival estimates of [redacted] The mean AUC varies between [redacted] months (Gompertz) and [redacted] months (lognormal).
The log-logistic, gamma and generalised gamma curves had similarly good statistical fit but there was [redacted] in the long-term survival predicted and mean AUC observed than in the weighted population: range [redacted] landmark survival at 120 months. The landmark survival estimates predicted by the economic model were within the range of what the EAG's clinical expert considered clinically plausible.

Enzalutamide – unweighted population

All curves provided reasonably [redacted] estimates at 12 months, 24 months, 36 months, 48 months, and 60 months, with a [redacted] between the most conservative and optimistic curves at 60 months although estimates were again less consistent at 120 months ([redacted] landmark survival). The mean AUC varies between [redacted]months (Gompertz) and [redacted]months (lognormal). The landmark survival estimates predicted by the economic model were [redacted] what the EAG's clinical expert considered clinically plausible: 0 – 10% at 10 years.

Similar to talazoparib with enzalutamide the generalised gamma, log-logistic and gamma curves had similarly good statistical fit but a reasonable deviation in long-term survivorship. The lognormal curve selected by the company provides a reasonably poor visual fit to the enzalutamide arm indicating that the use of curves may not have been appropriate.

Figure 9: Visual fit of overall survival extrapolation in comparison to enzalutamide

Graphic extracted from submitted Excel file

EAG commentary on OS curve selection

The EAG agreed with the company's base case curve choice for the MAIC weighted population (generalised gamma) as this provided a long-term survival estimate for olaparib with abiraterone in line with TA951 and the area between the curves is similar for 2 of the 3 options which provided a good statistical fit when comparing talazoparib with enzalutamide to olaparib with abiraterone (Table 27). Figure 11 demonstrates that in the weighted analysis after 5 years the implied hazard ratio is >1.

The EAG did not agree with the company's base case curve choice for the unweighted population (lognormal) as this had a poor statistical fit (5th best and AIC deviation of ~[redacted]) and a poor visual fit to the enzalutamide arm. It was also the most optimistic curve in terms of the mean AUC and [redacted] clinical expert advice from TA951: "OS of 8 – 10% at 10 years is expected using current care options" (predicted: [redacted] or to the EAG as part of this appraisal (expectation: 0 – 10%). The company stated this was chosen as "only the log-normal and exponential distributions did not exhibit kinks." The EAG could not see any visible kinks in the OS curves provided by the company for any of the other curve fits in Figure 6 of their response to clarification B2. Additionally, the EAG noted that altering the OS rather than rPFS curve selection to account for issues with curves crossing was not in line with the decision taken from the weighted data. The generalised gamma curve provided a better visual fit but had similar issues in terms of crossing with the selected rPFS curve (Table 29 and Table 30). The EAG

noted that when a less optimistic rPFS curve is selected (e.g. gamma) these issues are alleviated.

Figure 10 demonstrates that the lognormal curve results in a considerably more optimistic survival extrapolation for talazoparib with enzalutamide and also that the population selected makes some difference to the expected survival with predictions for the **PROpel** population being more favourable than for **TALAPRO-2**. Figure 11 demonstrates that in the unweighted analysis comparing to enzalutamide the treatment effect remains below 1 until around 10 years.

The EAG considered the generalised gamma curve more appropriate in terms of visual and statistical fit and use this in our base case

Figure 10: Overall survival: company base case estimates survivor function

Abbreviations: MAIC, matched adjusted indirect comparison; OS, overall survival
Note: model confirmed to function as intended as unweighted estimates for generalised gamma are the same in both the ola + abi and enza models

Figure 11: Overall survival: company base case estimates implied treatment effect

Abbreviations: MAIC, matched adjusted indirect comparison; OS, overall survival

Table 27: Incremental OS by curve selection

Curve	Incremental OS AUC (months) MAIC weighted population vs ola + abi	Incremental OS AUC (months) unweighted population vs ola + abi	Incremental OS AUC (months) unweighted population vs enza
Generalised gamma	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Key: AUC, area under the curve, OS, overall survival. Notes: The incremental OS AUC values were calculated from the model-predicted survival curves for each distribution, using the area under the undiscounted survival curve over a lifetime horizon

4.2.6.2. rPFS

Olaparib with abiraterone - MAIC weighted population

All curves [redacted] at 12 months, 24 months, however increased deviation was seen at 48 months, with a range of approximately [redacted] between the most conservative and

optimistic curves. The mean area under the curve (AUC) varies between [redacted] months (Gompertz) and [redacted] months (log-normal).

All curves had similarly good statistical fit (AIC difference of [redacted] and BIC difference [redacted] of between the best and worst fitting curves).

The exponential curve provided a landmark estimate that was [redacted] TA951 (28.2% at 48 months although it should be noted that all curves reported a [redacted] than in TA951 by [redacted] months). Following provision of unredacted data the EAG was able to compare 10 year survival between the two models. The generalised gamma curve selected in TA951 predicted 10 year rPFS of 8.9%. This compares to 17.5% from the log normal curve, 19.5% from generalised gamma and 16.4% from the log-logistic curve.

The generalised gamma curve was a less optimistic fit to the data for olaparib with abiraterone (3rd most optimistic) with again two rough clusters of curves observed – a more optimistic cluster (lognormal, loglogistic, generalised gamma) and a less optimistic cluster (Weibull, gamma, exponential, Gompertz).

The EAGs clinical expert considered a plausible range for rPFS for both olaparib with abiraterone and talazoparib with enzalutamide to be 0 – 10%.

Talazoparib with enzalutamide - MAIC weighted population

All curves provided [redacted] at 12 months, 24 months, 36 months, and 48 months, with a range of approximately [redacted] between the most conservative and optimistic curves. The mean AUC varied between [redacted] months (Gamma) and [redacted] months (generalised gamma). The fitted curves again presented in roughly two clusters – a more optimistic cluster (lognormal, loglogistic, generalised gamma, Gompertz) and a less optimistic cluster (Weibull, gamma, exponential).

The lognormal and generalised gamma curves had similarly good statistical fit. Other curves had similar and somewhat less good statistic fit (AIC difference of [redacted] and BIC difference [redacted] of between the best and worst fitting curves).

The company originally referenced TA951 for their rationale for selection of the generalised gamma curve. In TA951 the company selected the generalised gamma curve for the base-case analysis as this model was “marginally less optimistic than the other models”, this was not the case here. The generalised gamma curve was the most optimistic of the fitted curves. Figure 8 in the CS demonstrated that predicted rPFS was higher than predicted OS from around [redacted]

(~[redacted] of patients remained alive at this timepoint). The timepoints at which each of the selected rPFS curves cross the selected OS curve was provided in Table 28.

The companies updated selection (lognormal) still resulted in the rPFS and OS curves crossing but at a later timepoint when only [redacted] of patients remained alive and provided a less optimistic fit than the generalised gamma. The same was true for the loglogistic curve.

Table 28: Timing of rPFS crossing OS (TALA + ENZA arm)

Curve	Curve crossing at time point (years) / % remaining in rPFS	AIC / BIC	Incremental rPFS AUC (months) vs ola + abi (weighted)
Generalised gamma	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike Information Criterion, AUC, area under the curve, BIC, Bayesian Information Criterion, OS, overall survival, rPFS, radiographic progression-free survival. Notes: incremental rPFS AUC values were calculated from model-predicted survival curves for each distribution by calculating the area under the undiscounted rPFS curve over a lifetime horizon.

Talazoparib with enzalutamide – unweighted population

All curves [redacted] at 12, 24 and 36 months, however [redacted] was seen at 120 months, with a landmark range of [redacted] The mean area under the curve (AUC) varied between [redacted] months (gamma) and [redacted] months (Gompertz).

As with the weighted data the lognormal and generalised gamma curves had similarly good statistical fit. Other curves had similar and somewhat less good statistic fit. The generalised gamma curve produced a more optimistic long-term estimate than the other curves with the lognormal and log-logistic providing similar estimates and all other curves clustering with a much lower expected survival.

Enzalutamide – unweighted population

The landmark survival data provided by the company in Table 3 of the response to CQ B2 did not align to the visual provided in Figure 3 for 120-month rPFS. The EAG thought this was because the number of decimal points was incorrectly placed (by a factor of 10) for all curves

except the generalised gamma. The EAG has relied on Figure 3 for interpretation as this aligns with the economic model. There are 2 clusters of survival curves: a more optimistic cluster (generalised gamma, log-normal, log-logistic, Gompertz) with the remaining curves providing less optimistic estimates.

In TA951 the generalised gamma curve used in the FAD predicted rPFS of 37.3% at 24 months, 16.5% at 48 months and 3% at 120 months (unredacted data provided by NICE). This was based upon abiraterone data but was considered generalisable to enzalutamide data. The EAG noted that this is more in line with the less optimistic cluster of survival curves and therefore tested the impact of using the gamma curve (least optimistic) in scenario analysis.

The EAG did, however, note that rPFS was lower in **COU-AA-302** trial than in **TALAPRO-2** (comparing abiraterone and enzalutamide) which could be due to differences in the patient population enrolling in the trial or other factors and therefore the relevance of absolute estimates from TA951 using this population when applied to this appraisal are questionable (Figure 12 overlays the Kaplan Meier and curve fits presented in TA951 with the Kaplan Meier data from **TALAPRO-2**). Clinical expert advice to the EAG was, however, that few patients receiving enzalutamide would be expected to still be progression free at 10 years (0 – 5%).

The EAG also noted that the more optimistic cluster crossed the company's selected OS curve relatively early on in the time horizon and when a reasonable proportion of patients remained in PFS (~[redacted]). This was also true (and in fact potentially more so) for the generalised gamma curve which provided

Figure 12. KM and rPFS parametric extrapolation models for abiraterone vs KM for enzalutamide

Table 29: Timing of rPFS crossing OS ENZA monotherapy model (TALA + ENZA arm; lognormal for OS)

Curve	Curve crossing at time point (years) / % remaining in rPFS	AIC / BIC	Incremental rPFS AUC (months) vs enza
Generalised gamma			
Lognormal			
Gompertz			
Loglogistic			
Weibull			
Exponential			
Gamma			

Key: AIC, Akaike Information Criterion, AUC, area under the curve, BIC, Bayesian Information Criterion, OS, overall survival, rPFS, radiographic progression-free survival. Notes: incremental rPFS AUC values were calculated from model-predicted survival curves for each distribution by calculating the area under the undiscounted rPFS curve over a lifetime horizon.

Table 30: Timing of rPFS crossing OS ENZA monotherapy model (TALA + ENZA arm; generalised gamma for OS)

Curve	Curve crossing at time point (years) / % remaining in rPFS	AIC / BIC	Incremental rPFS AUC (months) vs enza
Generalised gamma	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike Information Criterion, AUC, area under the curve, BIC, Bayesian Information Criterion, OS, overall survival, rPFS, radiographic progression-free survival. Notes: incremental rPFS AUC values were calculated from model-predicted survival curves for each distribution by calculating the area under the undiscounted rPFS curve over a lifetime horizon.

EAG commentary on rPFS curve selection

In the MAIC weighted population the EAG agreed that the lognormal curve selected in the updated company base case provided a more reasonable estimate. The EAG also considered that the loglogistic curve provided a plausible estimate. Figure 13 demonstrates that in the unweighted analysis comparing to enzalutamide the treatment effect remains below 1 until around 5 years.

In the unweighted population the EAG also broadly agreed that the lognormal curve selected in the company base case provided a reasonable estimate when assessed independently of the OS fit selected. Figure 13**Error! Reference source not found.** demonstrates that in the unweighted analysis comparing to enzalutamide the treatment effect remains below 1 indefinitely. This was considered reasonable given the separation of the curves within trial and the fact that the effect was not increasing over time. However, given that this selection results in OS and rPFS crossing relatively early on in the model which was not considered plausible the EAG preferred the gamma curve in our base case. This provides a more conservative estimate in line with TA951 and clinical expert advice to the EAG.

Figure 13: Progression-free survival: company base case estimates implied treatment effect

Abbreviations: MAIC, matched adjusted indirect comparison; rPFS, radiographic progression-free survival

4.2.6.3. TTD

TTD was presented only for the unweighted population.

Olaparib with abiraterone

The company assumed that rPFS and TTD were equal for olaparib with abiraterone on the basis that there was published evidence from Clarke et al 2022 and the CADTH appraisal of olaparib with abiraterone demonstrated consistency between TTD and rPFS in **PROpel**, which supported the assumption that TTD is equal to rPFS for olaparib with abiraterone.[40,55]

The company stated that the TTD data presented in their addendum (Table 15) comes from the same datacut as the Clarke et al. 2022 abstract (CQ C1). This is not the case as the CADTH appraisal which is the source of this data reports information from datacut off 3 whereas Clarke et al report datacut off 1. CADTH amended the distribution used, as the original distribution which assumed 12% of people receiving olaparib with abiraterone continued to experience rPFS

benefit despite treatment discontinuation was seen to lack face validity. CADTH did not assume TTD was equal to PFS. The CADTH appraisal referenced also provided information on modelled TTD values for 15 and 20 years vs modelled rPFS for 15 and 20 years in the CADTH base case. This indicated that CADTH assumed a lower TTD than rPFS: rPFS at 15 years was 12% and at 20 years is 7% compared to landmark TTD of 5% and 3%.

Talazoparib with enzalutamide

The company supplied TTD for talazoparib with enzalutamide in response to a clarification question (B7). Data was supplied without adjustment to match the population in the MAIC as a pragmatic solution as insufficient time was available to produce this analysis.

The EAG checked the life years predicted in rPFS in order to determine how much of a difference the population was likely to make. The model predicted [redacted] years in the weighted population and [redacted] in the unweighted population using the lognormal for OS and [redacted] in the unweighted population using the generalised gamma for OS; differences of ~[redacted] and ~[redacted] when comparing to the MAIC weighted population. As rPFS was [redacted] in the unweighted analysis than in the weighted analysis the use of TTD from the unweighted population in the MAIC weighted analysis is expected to [redacted] TTD.

TTD was modelled separately for talazoparib and enzalutamide with the higher proportion remaining on treatment used to represent the percentage of patients continuing the combination in order to cost resource use.

The log-logistic distribution was selected for both talazoparib and enzalutamide TTD. The company stated that this was based on an assessment of statistical fit using AIC and BIC. This had the largest mean AUC for both components of the combination (Table 6 company response to CQ B2). The company applied a limiter to avoid patients remaining on treatment post-progression in the model. This, however, did not apply until [redacted] for enzalutamide and [redacted] for talazoparib at which point less than [redacted] of patients remain on treatment.

Enzalutamide

The log-logistic distribution was also selected for TTD for enzalutamide. This had the best statistical fit and largest mean AUC for both components of the combination (Table 6 company response to CQ B2).

Comparison of TTD and rPFS

Figure 14 and Figure 15 show the visual fit of the TTD curves to the Kaplan Meier data which is considered reasonable and also the difference between rPFS and TTD using both weighted and unweighted rPFS data. These clearly show the use of unweighted data for TTD introduces non-negligible bias

Figure 14: Comparison of TTD and PFS

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

Figure 15: TTD KM vs curve

Abbreviations: PBO, placebo; rPFS, radiographic progression-free survival

EAG commentary on TTD assumptions

The EAG considered the use of the log-logistic curve in the unweighted analysis for all treatments reasonable.

In comparison to olaparib with abiraterone, however, the company's assumptions resulted in a mean time on first line treatment of [redacted] months for talazoparib as part of the combination compared to [redacted] for olaparib. Given that rPFS was shorter for olaparib this did not appear to be plausible

The EAG considered that the assumptions made for TTD biased in favour of talazoparib with enzalutamide. This bias came from two sources:

- Assumption that TTD = rPFS for olaparib with abiraterone and not talazoparib with enzalutamide which did not align with the prior NICE or CADTH appraisal for olaparib with abiraterone
- Use of unweighted data (rPFS was longer in the weighted dataset and therefore TTD would also be expected to be longer)

Clinical expert advice to the EAG was that the TTD / rPFS relationship would be expected to be similar for olaparib with abiraterone and talazoparib with enzalutamide. The EAG's experts also considered that in real-world practice they would not expect much difference between TTD and rPFS.

In the EAG base case we assumed that the relationship between TTD and rPFS observed for talazoparib applied to olaparib and that the relationship between TTD and rPFS observed for enzalutamide applied to abiraterone. We present scenario analyses assuming TTD is equal to rPFS and using the hazard ratio from the original NMA for rPFS to create a proxy TTD curve for olaparib with abiraterone based upon the data for talazoparib with enzalutamide.

4.2.6.4. Post progression: subsequent treatment vs palliative care

The distribution of subsequent treatments included in the model was based on TA951 (elicited from six clinical experts; Table 31). It was assumed to be the same for all treatments. The company did not state the exact source, but we assume it was taken from Table 41 of the TA951 CS which reports data from Leith 2022[56] removing the possibility to use abiraterone, enzalutamide, mitoxantrone and Sipuleucel-T. The company then also assume that the market share post enzalutamide involves removing the possibility to use olaparib monotherapy.

In TA951, the experts stated that retreatment with abiraterone or enzalutamide was not permitted in UK clinical practice following disease progression on abiraterone or enzalutamide. The EAG asked Peter Clark to check if this remained the case following the availability of generic abiraterone, he stated that abiraterone would not be used after enzalutamide as the benefit for sequential androgen receptor inhibitor therapy after disease progression on a previous androgen receptor inhibitor therapy is low. This aligned with clinical expert feedback to the EAG and company as part of this appraisal.

The EAG note that olaparib is recommended, within its marketing authorisation, as an option for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) in adults (TA887) and therefore the costs associated with subsequent treatment with abiraterone and enzalutamide may be somewhat underestimated due to the exclusion of olaparib monotherapy. Scenario analysis was conducted to test the impact of this assumption.

Clinical expert advice to the EAG was that the proportion of patients eligible for docetaxel (and therefore use of this over cabazitaxel) would be expected to increase due to reduced use of

docetaxel in earlier treatment in mHSPC. This would only be expected to have a minor impact due to the low cost of both treatments.

Treatment durations for the subsequent treatments (Table 31) were based on published data from studies conducted prior to the availability of talazoparib with enzalutamide or olaparib with abiraterone as first-line therapy. The methods used to identify these studies were not described.

Table 31: Subsequent treatment distributions (CS Tables 30 and 32)

Subsequent treatment	Talazoparib with enzalutamide	Olaparib with abiraterone	Treatment duration (months)	PFS	Source
Docetaxel	50.0	50.0	5.9	NR	Tannock et al. (2004) [57]First-line mCRPC between 2000 and 2002
Cabazitaxel	29.1	29.1	5.1	8.0	de Wit et al. (2019)[58]
Carboplatin	3.5	3.5	2.1	Time to PSA progression: 2.1	Pemberton et al. (2024)[59]
Radium-223	17.5	17.5	5.5	Time to progression ALP: NE PSA: 3.6	Xofigo SmPC (2024)[60]

Key: ALP, alkaline phosphatase; CS, company submission; mCPRC, metastatic castration-resistant prostate cancer; NE, not estimable; NR, not reported; PFS, progression free survival; PSA, prostate-specific antigen; SmPC, Summary of Product Characteristics

The use of the number of cycles of treatment reported in the Tannock et al paper to calculate the time to receipt of palliative care was inappropriate as patients in that trial were scheduled to receive either up to 10 cycles of docetaxel administered every three weeks or 5 six-week cycles of docetaxel administered weekly. Stopping treatment may therefore not be an indication of treatment no longer working (46% of patients completed treatment with 3-weekly docetaxel). The same was true for Radium-223 which is given for a maximum of six injections.

The EAG calculated the time spent in each health state using the company base case economic model (Table 32). This indicated that the majority of time post progression was assumed to be in palliative care:

[redacted]

Table 32: Time spent by line of treatment in the economic model

	Talazoparib with enzalutamide (MAIC weighted)	Olaparib with abiraterone (MAIC weighted)	Talazoparib with enzalutamide (unweighted)	Enzalutamide (unweighted))
Time spent on 1st line treatment	[redacted]	[redacted]	[redacted]	[redacted]
Time spent on 2nd line treatment	[redacted]	[redacted]	[redacted]	[redacted]
Time spent in palliative care	[redacted]	[redacted]	[redacted]	[redacted]
% of time receiving 2nd line treatment in the progressed group	[redacted]	[redacted]	[redacted]	[redacted]
% of time receiving palliative care in the progressed group	[redacted]	[redacted]	[redacted]	[redacted]

Key: MAIC, matched adjusted indirect comparison

Table 31 shows that in the one study where PFS was reported this was longer than the reported treatment duration. Additionally, it should be noted that multiple lines of subsequent treatment are possible and therefore assuming patients go directly to palliative care after stopping a first treatment was not reasonable.

Clinical expert advice to the EAG was that the proportion of time spent in palliative care would be expected to be higher for talazoparib with enzalutamide relative to olaparib with abiraterone as patients receiving this combination take longer to progress and there is a higher toxicity burden with talazoparib with enzalutamide meaning that patients are likely to be less fit for further therapy once they progress. Clinical expert advice to the company was mixed in relation to the reasonableness of model estimates for the proportion of time spent receiving palliative care (CQ B14).

The durations assigned to subsequent treatments in TA951 did not impact on QALYs and costs in the same manner they do in this model as the TA951 model assumed one utility value for the entire progressed disease state and did not apply costs for palliative care.

EAG commentary on post progression assumptions

The EAG did not make any amendments to the assumptions around the split of time spent post progression in palliative care vs subsequent treatment in our base case as clinical expert feedback was mixed and a number of amendments were made already which limited the impact of this parameter. In particular:

- EAG base case: assumed one utility value for the entire progressed disease state in line with TA951
- Revised company base: assumed a more reasonable cost for palliative care

We provided scenario analysis testing the impact of reducing the time spent incurring a palliative care cost by 10% and 20%, given the issues with assuming the time on subsequent treatment is the same as the time to progression on subsequent treatment for treatments with a fixed duration of treatment.

4.2.7. Health-related quality of life

4.2.7.1. Impact of health state

HRQoL was measured in **TALAPRO-2** using EQ-5D-5L which was mapped to the EQ-5D-3L indices using the crosswalk algorithm described by Hernandez-Alava et al. 2022, in line with the NICE reference case.[61,62] A linear mixed-effects repeated measures model was used to predict EQ-5D utilities. Several fixed effects were considered, including planned treatment, time of visit (since randomisation), age, baseline utility, baseline Eastern Cooperative Oncology Group (ECOG) status, planned treatment, and an interaction term between planned treatment and health state. The final fitted model assumed the same utility for both treatment arms [redacted] for rPFS which [redacted] with previous submissions. Post progression utilities were not included in the economic model due to low sample size ([redacted]) observations. Follow-up was planned to continue every 12 weeks after centrally determined radiographic progression until end of study therefore it is unclear why the number of observations was so low; this may indicate a high volume of missing data.

Post progression utilities were instead taken from TA377 which used the weighted mean utility across two papers: Wolff 2012[52] (0.66±0.30 for patients who have had chemotherapy in the past and 0.64±0.31 for patients on chemotherapy) and Diels 2014[53] (0.69 for all patients with mCRPC in the UK). The modelled utilities for the first and second states post progression were a weighted mean of these utility weights; 0.658 and 0.612, respectively. The company in their submission only used the former of these and did not include a second line of treatment post progression assuming patients instead immediately receive palliative care. The palliative care utility used was again taken from TA377 which used Sandblom 2004 (utility: 0.5).

Diels 2014 was a mapping study from FACT-P to EQ-5D including 602 people from a cross-sectional, observational study across six European countries including the UK. Utility values

were generated using the UK-specific EQ-5D value set. At study inclusion, 39% of patients were chemotherapy naïve, 37% were undergoing chemotherapy, and 24% were post-chemotherapy.

Wolff 2012 was an abstract reported at ASCO GU and as such limited information was available. The focus of the abstract was hormone-naive and hormonally pretreated patients with prostate cancer treated with degarelix which is a GnRH-antagonist used in hormone-sensitive prostate cancer. The abstract did not report the utility values used in TA377 and therefore we assumed the manufacturer had access to the poster which was not available online.

Sandblom 2004 was a Swedish study which reported information on quality of life in the year immediately prior to death for people who died before 1 January 2001. The index used was unclear. The paper reported a mean EQ-5D index score of 0.538±0.077 for people who died of prostate cancer (n=66) and 0.564±0.067 for those who died of other causes (n=100). None of the people were receiving chemotherapy at the time of the questionnaire. A decrease in health-related quality of life was seen during the final year of life, especially during the final 4 months.

The company conducted an update to their literature review in response to CQ B1. This found 3 economic evaluations, none of which addressed a UK context, two of which were unclear as to which line of treatment they addressed (Zeng et al 2022[46], Goudarzi et al 2024[47]) and the final of which was an abstract which cited unreferenced previous literature as the source of inputs (Duru et al. 2024[45]).

EAG additional searches (Section 4.1) found an additional source (a systematic review and meta-analysis published by Castro et al in late 2024 just after the companies search date) and in addition the company responsible for the data contained in TA951 agreed to remove the redaction related to utility values. The Castro 2024 paper found that for economic modelling studies in the 1st line setting, the range of health state utility values reported for people who were progression free or had stable disease was 0.63 – 0.844, compared to 0.65 – 0.715 for progressive disease. Castro 2024 additionally conducted a meta-analysis of baseline utility values for 1st and 2nd line and later studies.

Table 33 provides a comparison of the utility values in the company's model compared to those used in TA951 and the Castro 2024 paper.

Table 33: Comparison of utility values between company model, TA951[63] and Castro 2024[51]

	Company model	TA951	Castro 2024, economic modelling studies	Castro 2024, random effects model, baseline values
Pre-progression	[redacted]	0.8143 (0.8009, 0.8277)	0.63 – 0.844	0.79 (0.75, 0.84) – 1st line
Post-progression	0.658	0.7754 (0.7528, 0.7980)	0.65 – 0.715	0.69 (0.67, 0.71) – 2nd line plus
Palliative care	0.500			

Notes: 95% confidence interval presented in brackets, range provided for the economic modelling studies identified by Castro 2024

NICE also provided unredacted utility values from TA887 (olaparib in previously treated patients BRCA mutation-positive patients) which included a utility value of 0.7063 whilst progression-free and 0.6298 when progressed based upon the prior taxane subgroup of Cohort A + B of **PROfound** (which also allowed prior new hormonal agent use). These most closely align with the post-progression health state and align well with the utilities in the Castro 2024[51] paper and less well with TA951[63] although they are likely for a somewhat later line of treatment.

EAG commentary

The EAG was concerned that the utilities used in the post-progression state in the company base case were from very historic sources some of which are of low quality and do not meet the NICE reference case. When compared to the data used in TA951[63] (which came from **PROpel**) the values used in the company's model were considerably lower. Similarly, they are lower than the majority of the utility values identified in prior models in the Castro 2024[51] systematic review for the post-progression state and the utilities used in TA887 which includes only previously treated patients. Given these concerns the EAG used the data from TA951 in the EAG base case and use the Castro 2024 baseline utility values in sensitivity analysis as although they do not provide ideal data (baseline rather than health-state utility values) they provide a plausible estimate in-keeping with the range of health-state utility values identified in the literature review. The EAG used one utility value for the entire post progression state and does not apply a separate value to patients receiving palliative care.

4.2.7.2. Impact of adverse events

AE data were naively sourced from **TALAPRO-2** and **PROpel** for talazoparib with enzalutamide and olaparib with abiraterone. In line with the original CS, the CUA accounts for the impact of all Grade ≥3 treatment-related AEs occurring in ≥5% of patients receiving treatment across either treatment arm of their respective studies (Table 16 CS). The same criteria were applied when using **TALAPRO-2** data for the comparison to enzalutamide resulting in some differences in the AEs included (hypertension included and VTE excluded).

Adverse events had very limited impact on modelled QALYs. The difference in incremental discounted QALYs due to AEs was [redacted] in comparison to olaparib with abiraterone due to limited impact being assumed for the adverse events with the most difference between the treatment arms (disutility -0.02 and 14 days duration). While in the enzalutamide comparison, QALY loss due to AEs was slightly lower for enzalutamide, translating into an incremental gain of [redacted] discounted QALYs in its favour. These assumptions were taken from the company base case in TA951. The EAG for this appraisal did not agree with these assumptions but did note that the alternative they tested (unfortunately redacted) only had a minor impact on cost-effectiveness.

"The EAG also notes that the AE-specific disutilities sourced by the company are very small. This may mean the model inadequately represents the impact of the differential toxicity profile of the alternative treatment options, particularly when combined with the 14-day assumed AE duration. The EAG prefers that AE durations are based on those observed in the **PROpel** trial, which in a number of cases are many times longer than the 14 days assumed in the company's base-case."

Clinical expert advice to ourselves, however, considered that the assumptions made were mostly reasonable as leukopaenia and neutropaenia alone are rarely symptomatic and whilst anaemia can result in fatigue it can usually be managed as a semi-elective day case procedure with packed red cell transfusion. Venous thromboembolic events were considered most likely to result in a HRQL decrement as treatment may be lifelong in this setting which was in line with the assumptions made.

Given the above we considered the company's assumptions reasonable.

4.2.7.3. Impact of SREs

SRE frequency data was stated to be naively sourced from **TALAPRO-2** and **PROpel**. This was not actually the case as TA951 (which was used for olaparib with abiraterone data) actually used data from TA831 which itself pooled data from three historical sources (**ALSYMPCA**, **COU-AA-301** and **AFFIRM**; see Table 32 on page 145 of the committee papers pdf). The use of these historical sources was more reasonable in TA951 as no difference between therapies was assumed as SREs were considered to be a result of disease progression, rather than the therapy received. Additionally, the method used to calculate the proportions appeared to be different (TA951 calculated SRE events as the number of events divided by the number of non-fatal progression events). The EAG in TA951 did not consider the impact to be well accounted for as SREs (as in this model) had only a very small effect upon QALYs which did not align with the substantially lower baseline utility observed in **PROfound** which the company in that appraisal considered was due to the high rate SREs.

Clinical expert advice to the EAG was that skeletal related events can be related to treatment (in the case of fractures particularly antigen deprivation treatment) but overall cancer (and disease progression) is the biggest contributor to these effects. This aligns with clinical expert advice to the company (CQ B8). Additionally, the historical trials used in TA831 and then TA951 were not considered relevant as the patient population and management of bone health was different when these trials were conducted (over a decade ago).

The company's base case assumed that the rate of SREs was [redacted] for olaparib with abiraterone than talazoparib with enzalutamide ([redacted] times higher for spinal cord compression and [redacted] times higher for radiation to bone). This did not align with clinical expert advice received.

Given the above the EAG did not consider the company's method for inclusion of SREs in the model to be robust and excluded SREs from the EAG base case. The EAG also present a scenario analysis assuming SREs occur at the same rate as in **TALAPRO-2** for all arms.

4.2.7.4. Age adjustment

Age-adjusted utilities were implemented using the methods described in Hernandez-Alava (2022)[62] in line with DSU guidance. The EAG considered this appropriate.

4.2.8. Resources and costs

4.2.8.1. Drug and administration costs

Drug and administration costs were based upon BNF, eMIT and dosing information presented in product SmPCs. The EAG noted that there were discounts in place enzalutamide, olaparib and abiraterone which were confidential and were therefore not included in the company's analysis. Results with these discounts included are presented for Committee members in the cPAS appendix to this report.

The EAG noted that since TA951[63] abiraterone has become available as a generic treatment with a considerably reduced cost (£76.91 for a pack of 56 x 500mg tablets[64]) which results in a cost per month of £174 for abiraterone with prednisolone compared to [redacted] per month for enzalutamide at list price.

The EAG also noted that the primary patent for enzalutamide in the UK is set to expire in 2026.[65] In June 2024, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended granting a marketing authorisation for Enzalutamide Viatris,[66] a generic version of enzalutamide indicating that a generic version may be available soon after patent expiry. Given the change in price seen following patent expiry for abiraterone this could be expected to considerably influence the cost-effectiveness case.

The company included the cost of ADT (goserelin) in response to clarification questions (B12) as clinical expert advisors to the EAG stated would be given to people except in the very terminal phase. The EAG checked with clinical expert advisors which ADT treatments were most frequently used. One clinical expert sent data showing the breakdown of ADT use in their trust which indicated 46% used triptorelin, 33% leuprorelin and 20% goserelin and a small minority (<1%) used buserelin. They provided the total daily usage and total daily cost for each regimen for their trust. Based upon this data the mean cost per month was £72; similar to the company's estimate of £76 which was therefore considered reasonable.

The company assumed in their original base case that all patients receive the full planned dose of treatment whilst on treatment (RDI = 100%).

In response to clarification questions (B11) the company provided an updated analysis using the proportion of use of each dose within **TALAPRO-2** to calculate costs for talazoparib and enzalutamide. Based upon these calculations the company estimate a weighted average list price of [redacted], which equates to an RDI of [redacted]. For enzalutamide as part of the combination

the company maintain use of the median RDI ([redacted]) and similarly use the median for monotherapy ([redacted]). For olaparib with abiraterone only the median RDI for the entire combination was available (98.20%). Although it was likely based upon the data seen in **TALAPRO-2** that more doses are reduced / missed for olaparib relative to abiraterone the price of both 100mg and 50mg doses of olaparib was the same and therefore the use of the RDI presented can be considered reasonable. The use of the median RDI for enzalutamide, whilst it was not ideal as economic principles would prefer the mean, was acceptable to align with the data available for olaparib with abiraterone.

The company originally assumed no administration cost for oral therapies and that wastage was fully accounted for by not including a half cycle correction for time on treatment. In response to clarification questions (B12) the company included pharmacy dispensing costs based upon the NHS Electronic Drug Tariff website[67] and provided an updated scenario analysis assuming that only full packs are dispensed. The EAG considered this more reasonable and adopted this in our base case.

Otherwise, the EAG considered the dosing and costs used within the model to be appropriate.

4.2.8.2. Subsequent treatment costs

Subsequent treatment costs were sourced from eMIT, the BNF and NHS reference costs and were applied to the treatment durations in Table 31. The EAG noted that the company model took the cost of cabazitaxel from the BNF when a cost was available in eMIT of £272 per 60mg (less than 10% of the BNF cost). Otherwise, the costs were considered appropriate.

Administration costs were modelled using NHS reference costs code SB13Z (delivery of more complex parenteral chemotherapy at first attendance). This was considered appropriate.

Wastage was included in the model for IV drugs using method of moments with weight data based on Pfizer data on file (2022), which reported a mean weight of 82.54 kg and mean BSA of 1.99 m² for patients in Cohort 1 of **TALAPRO-2**. This was considered appropriate

4.2.8.3. Health state costs

Disease monitoring frequencies and proportions of patients undergoing disease monitoring were sourced from TA951,[18] Talzenna SmPC (2024),[68] and Xtandi SmPC (2024)[69]. The company assumed these are different for talazoparib with enzalutamide and olaparib with abiraterone.

The differences were more frequent complete blood tests with olaparib with abiraterone in the first 3 months, liver and kidney function tests included for olaparib with abiraterone and not talazoparib with enzalutamide, treatment toxicity monitoring included in the first 12 months for olaparib with abiraterone and not talazoparib with enzalutamide. Clinical expert opinion received by the EAG was that the long-term monitoring requirements would be the same for people on either treatment and that little difference in costs is expected initially. The EAG checked the cost difference in the short term and considered this to be minimal and therefore in line with clinical advice.

The company assumed that drug specific monitoring is not required for enzalutamide and that overall monitoring costs were reduced which appears plausible (£180 vs £315 per month in the first 3 months and £109 vs £181 afterwards).

4.2.8.4. Adverse event costs

Adverse event costs were lower in the addendum for the cost utility analysis than in the cost comparison CS. The company provided comparison of the cost codes used between the original and new submission and TA951, made a minor amendment to the cost for anaemia and explained the discrepancies in response to clarification questions (B13).

The EAG checked the costs used with our clinical expert. They considered the assumptions made generally reasonable with the following exceptions:

- Symptomatic G3+ neutropenia would require an acute admission which would be more costly
- Thromboembolic events which by definition require urgent medical management including in some cases acute admission of at least for 24hours until stabilised.

Given that these events were less frequent in the talazoparib with enzalutamide arm in comparison to olaparib with abiraterone and rates were generally reasonably low the EAG did not explore additional scenarios as they would be expected to only have a minimal impact.

4.2.8.5. Palliative and terminal care costs

Following progression on subsequent treatments the model applies a palliative care cost of £676.80 per month based upon a source used in TA377 (Guest 2006[70]) inflated to the current year (from 2000). The company originally stated this was in line with the approach in TA951, however, the EAG can find no evidence of this. There was no reference to the paper in TA951

which only includes a one-off cost for terminal care of £2,170 based upon TA391 (based on expert estimates for resource use in the last month of life). At the clarification stage, the company acknowledged that this was an outdated source (CQ B16) and updated the model to use a model recent source (Round et al 2015[71]).

Round et al. 2015 reported a palliative care cost following the commencement of strong opioids (considered indicative of receipt of palliative care) of £9,415 for prostate cancer in the UK. This cost was based on both healthcare resource use (e.g., inpatient admissions, outpatient attendances, GP contacts) and social care resource use (e.g., home care, nursing home, residential care; all direct costs sourced from PSSRU). The EAG noted that some of the social care costs included may be paid for by the patient rather than PSS and therefore should not be included in the NICE reference case. The company applied this as a monthly cost based upon the expected survival time in palliative care reported in the paper (360 days) and then adjusted for inflation using estimates from the ONS.

Clinical expert advice to the EAG was that a reasonable proportion of patients will receive a significant burden of medication to manage symptoms and will often need some social or personal care to support activities of daily living, particularly when not supported by family members. They may then require acute admissions either to hospital, or to palliative care facilities despite best supportive management. On occasions patients would still receive palliative courses of radiotherapy for symptomatic sites and a proportion of patients would still have symptomatic skeletal events, which could result in prolonged disability which will increase their care costs substantially (this was, however, not expected to differ substantially between treatments). The latter of these costs would not be included in the current estimate.

The EAG considered the companies updated source of costs for palliative care to be reasonable and that the likely inclusion of some non-reference case costs for social care can be balanced against the exclusion of costs for palliative courses of radiotherapy.

The company also applied the terminal cost from TA951 in their updated model post clarification questions. The EAG considered this to be double counting as TA951 did not include both a palliative care cost and a terminal care cost and the types of resource use discussed as being included in the expert estimates used in that appraisal were covered within the palliative care costs presented by Round et al. 2015.

Given the above the EAG removed the terminal care cost from our base case. In addition, the source used for inflation adjustment was updated to the NHS Cost Inflation Index (NHSCII) published in the PSSRU 2024.

4.2.9. Validation

Outputs from economic analyses presented in previous relevant technology appraisals, namely TA951 and TA377, are redacted, therefore we are not able to compare outputs.

Validation of inputs was presented compared to TA951 where data were available in the earlier sections. Similarly, validation of curve fits compared to observed trial data has been presented in earlier sections.

4.2.10. Uncertainty

The company conducted probabilistic and deterministic sensitivity analyses on most model parameters. Where available, standard errors were derived from source data; otherwise, a default standard error of 20% of the base-case value was applied. Probabilities were modelled using beta distributions and costs using gamma distributions. Parameters fixed at 0% or 100% were not varied in the sensitivity analyses.

The EAG considered this a pragmatic and generally acceptable approach to characterising parameter uncertainty. However, two key limitations were identified. First, the company assigned a standard error to the discount rate. The EAG did not consider this appropriate, as the discount rate is a fixed methodological input rather than a parameter subject to uncertainty. Second, the company applied independent beta distributions to each of the proportions representing subsequent treatments. The EAG noted that this approach fails to reflect the compositional nature of these parameters, which must sum to one. A Dirichlet distribution would have been a more appropriate choice to capture the correlation

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

The results presented in this report incorporate the PAS discount for talazoparib and list prices for all other treatments. This report is accompanied by a confidential appendix that reports the results of the analyses when confidential prices for all other treatments are included.

The results reported are taken from the two models supplied by the company in response to clarification questions (one comparing to olaparib with abiraterone in the MAIC weighted population and the other comparing to enzalutamide in the unweighted population).

5.1.1. Base case results

5.1.1.1. Comparison with olaparib with abiraterone

The results reported by the company are shown in Table 34. The deterministic and probabilistic results are broadly similar with incremental QALYs of [redacted] and [redacted], respectively. ICERs have not been interpreted as only the talazoparib discount is incorporated.

Table 34: Company base case results vs olaparib with abiraterone

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Ola + abi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tala + enza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case					
Ola + abi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tala + enza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: abi, abiraterone; enza, enzalutamide; QALYs, quality adjusted life years; tala, talazoparib

5.1.1.2. Comparison with enzalutamide

Similarly, the deterministic and probabilistic results were broadly similar with incremental QALYs of [redacted] and [redacted], respectively.

Table 35: Company base case results vs enzalutamide

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Enza	[redacted]	[redacted]			
Tala + enza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company probabilistic base case					
Enza	[redacted]	[redacted]			
Tala + enza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: enza, enzalutamide; QALYs, quality adjusted life years; tala, talazoparib

5.2. Company's sensitivity analyses

The company undertook one-way sensitivity, probabilistic analysis and scenario analyses.

5.2.1. Deterministic sensitivity analyses

The parameter with the greatest impact on the incremental net monetary benefit in the comparison to olaparib with abiraterone was [redacted]. All other parameters had limited impact. In the company model in comparison to enzalutamide the parameter with the most impact was the [redacted], followed by [redacted]. The EAG considered this result unexpected and discovered that this was due to an error in the model. Following correction of this error the [redacted] and [redacted] were the most influential parameters (Figure 16).

Figure 16: Corrected OWSA in comparison to enzalutamide

[redacted]

5.2.2. Probabilistic sensitivity analysis

The model showed good convergence in both comparisons after approximately 200 iterations. Figure 17 demonstrates a relatively large spread of probabilistic samples including [redacted] in the South West quadrant (less effective, less costly). Figure 18 shows more certainty in the estimate for the within-trial analysis as would be expected.

Figure 17: Cost-effectiveness plane vs olaparib with abiraterone

Figure 18: Cost-effectiveness plane vs enzalutamide

5.2.3. Scenario analyses

The scenarios presented by the company with the greatest impact in the comparison to olaparib with abiraterone were the [redacted], [redacted], [redacted] and the [redacted] (Table 36).

Table 36: Scenario analysis vs olaparib with abiraterone

	Inc. Costs	Inc. QALYs	ICER (per QALY)	Difference in ICER
Base Case	[redacted]	[redacted]	[redacted]	[redacted]
FP NMA for rPFS, constant HR for OS	[redacted]	[redacted]	[redacted]	[redacted]
TALAPRO-2 OS: log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TTD: Set equal to rPFS	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and health outcomes (%/year): 0	[redacted]	[redacted]	[redacted]	[redacted]
TALAPRO-2 OS: log-normal distribution	[redacted]	[redacted]	[redacted]	[redacted]
Drug monitoring frequency source: Drug specific SmPCs	[redacted]	[redacted]	[redacted]	[redacted]
TALAPRO-2 rPFS: log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and health outcomes (%/year): 5	[redacted]	[redacted]	[redacted]	[redacted]
Age-adjusted utilities not applied	[redacted]	[redacted]	[redacted]	[redacted]
Oral wastage: Incurred explicitly - Drugs administered only in full packs	[redacted]	[redacted]	[redacted]	[redacted]
Consider wastage? No	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall surival; QALY, quality-adjusted life-year; rPFS, radiographic progression-free survival; SmPC, summary of product characteristics; TTD, time to discontinuation

Notes: taken directly from the Excel model and Table 11 of the response to CQ A6 for the companies FP NMA scenario

The only scenario with any meaningful impact in the comparison to enzalutamide was the assumption made for TTD (Table 37).

Table 37: Scenario analysis vs enzalutamide

	Inc. Costs	Inc. QALYs	ICER (per QALY)	Difference
Base Case	[redacted]	[redacted]	[redacted]	[redacted]
TTD: Set equal to rPFS	[redacted]	[redacted]	[redacted]	[redacted]
TALAPRO-2 OS: log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
TALAPRO-2 rPFS: log-logistic distribution	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and health outcomes (%/year): 0	[redacted]	[redacted]	[redacted]	[redacted]
Age-adjusted utilities not applied	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for costs and health outcomes (%/year): 5	[redacted]	[redacted]	[redacted]	[redacted]

Consider wastage? No	[redacted]	[redacted]	[redacted]	[redacted]
Consider oral treatment wastage explicitly? Yes	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall surival; QALY, quality-adjusted life-year; rPFS, radiographic progression-free survival; TTD, time to discontinuation

Notes: taken directly from the Excel model

6. EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and explored the impact of parameter values, and assumptions, which the EAG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 provides a summary of the alternative assumptions explored by the EAG to test the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. Section 6.2.10 presents the EAGs base case, which represents what the EAG consider to be the most plausible and methodologically sound approach to assessing cost-effectiveness, based on NICE's reference case. Section 6.4 presents the impact of scenario analyses conducted to explore uncertainty within the EAG base case.

The results presented in this report incorporate the PAS discount for talazoparib and list prices for all other treatments. This report is accompanied by a confidential appendix that reports the results of the analyses when confidential prices for all other treatments are included.

Results are presented deterministically for each adjustment made by the EAG due to the slow speed of the PSA in the executable model(estimated run time ~30 minutes). PSA is presented for the EAG base case only.

6.1. EAG corrections and adjustments to the company's base case model

A small number of errors were identified in the company models provided post clarification questions. Firstly, the cost for cabazitaxel and Radium-223 was taken from the BNF rather than eMIT, secondly uncertainty around the price discount for talazoparib was incorrectly incorporated in PSA, thirdly the company used a Beta distribution for correlated parameters relating to subsequent treatments in the PSA, fourthly we updated the source used for inflation adjustment to the NHS Cost Inflation Index (NHSCII) to align with standard practice and finally an issue was identified with the OWSA setup in the model. Three parameters listed for inclusion in the OWSA on the "inputs" sheet were not present in the corresponding input parameter list on the "one-way-calc" sheet. As a result, the VBA module responsible for automating the OWSA pasted results that did not correspond with the correct parameter names, leading to a mismatch between parameters and results. This was resolved by adding the three missing parameters to

the input list on the "one-way-calc" sheet, and rerunning OWSA. These issues had limited impact on the assessment.

6.1.1. Comparison to olaparib with abiraterone in the MAIC weighted population

EAG corrections had a limited impact on the deterministic company base case in the comparison to olaparib with abiraterone (two out of five only applied to the PSA; Table 38).

Table 38: EAG-corrected company base case results vs olaparib with abiraterone

Preferred assumption	Treatment	Total costs (£)	Total QALYs	ICER	NMB WTP: £30,000 per QALY	+/- company base case
Company base case	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No SE around discount	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life cost corrected	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Update cost for Radium-223 dichloride to use eMIT from NICE pricing tracker	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Update cost for cabazitaxel to use eMIT from NICE pricing tracker	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dirichlet distribution for joint probabilities	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case	**TALA + ENZA**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI, abiraterone; EAG, external assessment group; eMIT, electronic marketing information tool; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OLA, olaparib; QALYs, quality adjusted life years; SE, standard error; TALA, talazoparib; WTP willingness to pay

6.1.2. Comparison to enzalutamide in the unweighted population

Similarly, EAG corrections had a limited impact on the deterministic company base case in the comparison to enzalutamide (Table 39).

Table 39: EAG-corrected company base case results vs enzalutamide

Preferred assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs	Inc. QALYs	ICER
Company base case	ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No SE around discount	ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life cost corrected	ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Update cost for Radium-223 dichloride to use eMIT from NICE pricing tracker	ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Update cost for cabazitaxel to use eMIT from NICE pricing tracker	ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dirichlet distribution for joint probabilities	ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG corrected company base case	**ENZA**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; eMIT, electronic marketing information tool; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; SE, standard error; TALA, talazoparib

6.1.3. Comparison to abiraterone with prednisolone

At the time of writing, abiraterone was considerably cheaper than enzalutamide and the EAG presents an analysis which compares to abiraterone assuming similar effectiveness and time on treatment to enzalutamide (an assumption made in a number of prior prostate cancer appraisals including TA951[63]). The companies' proportional hazards NMA showed abiraterone to have reduced OS and even further reduced rPFS (and therefore expected reduced time on treatment) in comparison to enzalutamide (Section 3.3.1). The CrIs overlapped in both cases (although

there is not much overlap for rPFS). The direction of bias in this comparison was therefore expected to be broadly in favour of talazoparib with enzalutamide.

EAG corrections had a limited impact on the comparison to abiraterone (Table 40). Individual steps were not shown as the only difference between this and the comparison to enzalutamide was the cost of the comparator treatment due to the assumption of equal effectiveness.

Table 40: EAG-corrected company base case results vs abiraterone

Preferred assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs	Inc. QALYs	ICER
Company base case (using abiraterone costs)	ABI	[redacted]	[redacted]			[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG-corrected company base case (using abiraterone costs)	ABI	[redacted]	[redacted]			[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI, abiraterone; EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; TALA, talazoparib

6.2. Exploratory and sensitivity analyses undertaken by the EAG

Given that two different Excel files were received by the EAG with the model comparing to enzalutamide provided on 15th May (3 weeks prior to delivery of the EAG report) the EAG conducted all planned scenario analysis on the comparison to olaparib with abiraterone and tested a more limited range of scenario analysis for the comparison to enzalutamide with scenario analysis selected based upon the scenarios with the most impact in the olaparib with abiraterone comparison.

6.2.1. Assumptions made for TTD

The EAG explored three scenarios to account for the biases in the company assumptions for TTD which underestimate the cost of talazoparib with enzalutamide relative to olaparib with abiraterone. Firstly (EAG base case) we assumed that between TTD and rPFS observed for talazoparib applied to olaparib and that the relationship between TTD and rPFS observed for enzalutamide applied to abiraterone. The EAG applied a scaling approach within the economic model. A time-varying hazard ratio was calculated based on the relationship between TTD and rPFS observed in the reference treatment arm. The TTD curve for olaparib was derived by scaling the olaparib rPFS curve using the TTD:rPFS ratio from talazoparib, while the TTD curve

for abiraterone was derived by applying the enzalutamide TTD:rPFS ratio to the abiraterone rPFS curve. This allowed for treatment-specific estimates of TTD that remain consistent with the clinical relationship observed between TTD and rPFS in **TALAPRO-2**.

Secondly (scenario analysis) we assumed TTD was equal to rPFS in line with the analysis originally presented by the company in the CS addendum. Finally, we applied the rPFS HR from the original company NMA ([redacted]) to the talazoparib with enzalutamide TTD curve to estimate TTD for olaparib with abiraterone.

Figure 19 compares the company assumption for TTD for olaparib with abiraterone (red line) with their assumption for talazoparib with enzalutamide (green line; talazoparib with enzalutamide has the lower TTD) versus the EAG base case for olaparib with abiraterone (blue line; olaparib with abiraterone has the lower TTD).

Figure 19: Comparison of assumptions made for TTD

6.2.2. Post progression utility

The EAG explored two scenarios to account for the post-progression utilities presented by the company being considered too low when compared to other data sources identified. Firstly (EAG base case) we used data taken from TA951 which was provided unredacted by NICE to

the EAG. Secondly (scenario analysis) we used data from Castro 2024. Both sources were applied multiplicatively keeping the utility in rPFS constant as the data from **TALAPRO-2** was considered most relevant to the rPFS health state.

Table 41: Multipliers used in EAG analysis for post progression utility

Source	Health state	Estimate	Multiplier
TA 951	Progression-free	0.8143	PD/PFS= 0.95
	Progressed disease	0.7754	
Castro et al 2024	Progression-free	0.79	PD/PFS= 0.87
	Progressed disease	0.69	

Table 42: Health state utilities used in EAG analysis for post progression utility

Health-state utility	Company submission	EAG base-case (TA 951)	Castro 2024 NMA
rPFS	[redacted]	[redacted]	[redacted]
PD while on 2L treatment	[redacted]	[redacted]	[redacted]
PD post-2L treatment	[redacted]	[redacted]	[redacted]

6.2.3. Skeletal related events

The EAG base case in the comparison to olaparib with abiraterone excluded skeletal related events as the EAG did not consider the company's method for inclusion of SREs in the model to be robust. The EAG also presented a scenario analysis assuming SREs occurred at the same rate as in **TALAPRO-2** for all arms which was in line with the assumption of independence from treatment type used in TA951.[63]

6.2.4. Drug costing

The EAG applied the company scenario which fully accounted for the cost of oral drug wastage in our base case. We tested the impact of assuming that the full planned dose was received for all treatments in scenario analysis.

6.2.5. Resource use

The EAG base case excluded terminal care costs due to double counting with palliative care costs. In scenario analysis we tested the impact of reducing the time spent incurring a palliative care cost by 10 and 20%; this scenario was provided as the company assumed that palliative

care costs were incurred as soon as patients come off treatment with a subsequent therapy which was unlikely to be correct as some of the treatments were only given for a fixed duration and additionally the sources of subsequent treatment durations were of relatively low quality.

6.2.6. Treatment effect

The EAG tested the impact of using the FP NMA for rPFS without changing the assumptions for OS. The EAG also presented a scenario using the original proportional hazards NMA in the unweighted population.

6.2.7. Assumptions made for rPFS

The EAG conducted a number of scenario analyses for rPFS. including generalised gamma, log-logistic and lognormal curves as the best fitting options according to statistical fit criteria and comparison to TA951 for olaparib with abiraterone.

In the comparison to enzalutamide we selected the gamma curve in the EAG base case as this better aligned with the rPFS estimates for current care from TA951[63] and clinical expert advice to the EAG and avoided the issues with the OS and rPFS curves crossing early on in the time horizon. We also tested generalised gamma, log-logistic and lognormal curves in scenario analysis.

6.2.8. Assumptions made for OS

The EAG also conducted a number of scenario analyses for OS. In the comparison to olaparib with abiraterone the EAG tested the impact of using the log-logistic and lognormal curves as the best fitting alternative curve options based upon statistical fit and comparison to TA951[63] and we tested the impact of assuming equal hazards between the two treatments at 5 and 10 year timepoints.

In the comparison to enzalutamide, we selected the lognormal curve in our base case as this provided a better statistical and visual fit and better alignment to clinical advice to the EAG in terms of landmark survival. We also tested log-logistic curves in scenario analysis.

6.2.9. Assumptions made for abiraterone effectiveness

During FAC, the company challenged the EAG's analysis comparing TALA+ENZA vs ABI, arguing that the use of ABI costs instead of ENZA costs is inappropriate. The company maintained that the EAG's naive assumption of equivalent efficacy between ABI and ENZA is

fundamentally flawed, as this assumption had already been refuted in TA951, where ENZA demonstrated superior efficacy over ABI.

In response, the EAG provided an analysis applying the ENZA vs ABI HR from TA951 (HR 1.19; 95% CrI: 1.10 to 1.30) to OS and rPFS to model the impact of assuming reduced effectiveness. The impact on TTD is implicitly captured as TTD is modelled based upon the relationship between TTD and rPFS.

The EAG also conducted threshold analysis to determine the HR needed in order for talazoparib with enzalutamide to be cost-effective at £20,000; £25,000 and £30,000 per QALY willingness to pay thresholds.

6.2.10. Assumptions made for subsequent treatment post enzalutamide

In this scenario the costs of subsequent treatment post ENZA were updated to include olaparib as a subsequent treatment option in the ENZA arm, reflecting its recommendation in TA887, where olaparib is approved within its marketing authorisation for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations following prior treatment with NHAs (e.g. abiraterone or enzalutamide). To do this, the EAG applied market share estimates for olaparib as a subsequent treatment based on data used in TA951, adjusting the remaining distribution of market shares accordingly. The duration of olaparib treatment was assumed to be 7.5 months, in line with TA951 assumptions.

6.3. EAG's preferred assumptions

6.3.1. Comparison to olaparib with abiraterone

The cost difference between olaparib with abiraterone and talazoparib with enzalutamide reduced from [redacted] in the corrected company base case to [redacted] in the deterministic EAG base case (confidential discounts only included for talazoparib; Table 43). The QALY gain reduced from [redacted] to [redacted]. The main driver of the cost differences was the assumptions made for TTD. The main driver of the QALY differences was the utility assumed post progression. Probabilistic analysis was consistent with the deterministic results.

Table 43: EAG's preferred model assumptions vs olaparib with abiraterone

Section in EAG report	Preferred assumption	Treatment	Total costs (£)	Total QALYs	ICER	NMB WTP: £30,000 per QALY	+/- company base case
6.1.1	EAG Corrected	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.2	Post progression utility from TA951	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.4	Drug wastage fully applied	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.3	Exclude SREs	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.5	Terminal care cost excluded	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.1	Adjusted TTD using comparative rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (deterministic)		**TALA + ENZA**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (probabilistic)		**TALA + ENZA**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI, abiraterone; EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OLA, olaparib; QALYs, quality adjusted life years; rPFS, radiographic progression-free survival; SE, standard error; SRE, skeletal-related event; TALA, talazoparib; TTD, time to discontinuation; WTP willingness to pay

Figure 20 demonstrated considerable uncertainty around the EAG base case in the comparison to olaparib with abiraterone in probabilistic analysis.

Figure 20: EAG base case cost-effectiveness plane vs olaparib with abiraterone

Figure 21 demonstrates that the key areas of remaining parameter uncertainty were the discount rate for costs, palliative care costs and the costs of second line treatment although model sensitivity to individual parameter uncertainty was limited.

Figure 21: EAG base case tornado diagram vs olaparib with abiraterone

6.3.2. Comparison to enzalutamide

The cost difference between enzalutamide monotherapy and talazoparib with enzalutamide increased marginally from [redacted] in the corrected company base case to [redacted] in the EAG

deterministic base case (confidential discounts only included for talazoparib; Table 44). The QALY gain reduced from [redacted] to [redacted]. The main driver of the differences were the assumptions made for the utility assumed post progression. Probabilistic analysis was broadly consistent with the deterministic results.

Table 44: EAG's preferred model assumptions vs enzalutamide

Section in EAG report	Preferred assumption	Treatment	Total costs (£)	Total QALYs	Inc costs	Inc QALYs	ICER
6.1.1	EAG Corrected	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.2	Post progression utility from TA951	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.4	Drug wastage fully applied	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.5	Terminal care cost excluded	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.8	Gen gamma OS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.7	Gamma rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (deterministic)		**TALA + ENZA**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (probabilistic)		**TALA + ENZA**	[redacted]	[redacted]			
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OS, overall survival; QALYs, quality adjusted life years; rPFS, radiographic progression-free survival; SE, standard error; TALA, talazoparib; TTD, time to discontinuation; WTP willingness to pay

Figure 22 demonstrates reduced uncertainty around the EAG base case in the comparison to olaparib with abiraterone in probabilistic analysis with the vast majority of samples indicating a QALY gain.

Figure 22: EAG base case cost-effectiveness plane vs enzalutamide

The model showed limited sensitivity to individual parameter uncertainty with the discount rates used coming top of the tornado diagram (Figure 23).

Figure 23: EAG base case tornado diagram vs enzalutamide

6.3.3. Comparison to abiraterone with prednisolone

The ICER increased considerably in the EAG base case comparison to abiraterone due to the lower drug costs associated with this treatment (Table 44). Individual steps and sensitivity analysis were not shown as the only difference between this and the comparison to enzalutamide was the drug price used for the comparator.

Table 45: EAG's preferred model assumptions vs abiraterone

Preferred assumption	Treatment	Total costs (£)	Total QALYs	Inc costs	Inc QALYs	ICER
EAG base case	ABI	[redacted]	[redacted]			[redacted]
	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI, abiraterone; EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; TALA, talazoparib

6.4. EAG scenario analyses

Exploratory analyses (Table 46) were conducted individually on top of the EAG base case. The model was sensitive to the assumptions made for TTD for olaparib with abiraterone and the type of analysis used to model the treatment effect. The model was robust to all other assumptions tested (note confidential discounts only included for talazoparib).

Table 46: EAG's scenario analysis vs olaparib with abiraterone

Section in EAG report	Preferred assumption	Treatment	Total costs (£)	Total QALYs	ICER	NMB WTP: £30,000 per QALY	+/- company base case
6.2.10	EAG Base Case	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.2	Post progression utility from Castro 2024	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.5	Reducing the time spent incurring a palliative care cost by 10%	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section in EAG report	Preferred assumption	Treatment	Total costs (£)	Total QALYs	ICER	NMB WTP: £30,000 per QALY	+/- company base case
6.2.5	Reducing the time spent incurring a palliative care cost by 20%	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.3	Assume SREs are the same rate on both arms using TALAPRO-2	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.4	Full planned dose cost for all treatments	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.1	Apply rPFS HR to TTD	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.8	Log-logistic for OS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.8	Lognormal for OS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.1	TTD equal to rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.7	Log logistic for rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.6	rPFS FP NMA	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.6	Original PH NMA OS and rPFS	OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI, abiraterone; EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OLA, olaparib; QALYs, quality adjusted life years; rPFS, radiographic progression-free survival; SE, standard error; SRE, skeletal-related event; TALA, talazoparib; TTD, time to discontinuation; WTP willingness to pay

The model demonstrated limited sensitivity to the scenarios tested in the comparison to enzalutamide monotherapy (Table 47). Given this, these scenario analyses were not conducted for the comparison to abiraterone.

Table 47: EAG's scenario analysis vs enzalutamide

Section in EAG report	Preferred assumption	Treatment	Total costs (£)	Total QALYs	Inc costs	Inc QALYs	ICER
6.2.10	EAG Base Case	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.2	Post progression utility from Castro 2024	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.5	Reducing the time spent incurring a palliative care cost by 10%	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.5	Reducing the time spent incurring a palliative care cost by 20%	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.4	Full planned dose cost for all treatments	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.7	Log-logistic rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.8	Log-logistic OS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.7	Generalised gamma rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.7	Lognormal rPFS	TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6.2.10	Including the cost of olaparib post enzalutamide	ENZA	[redacted]	[redacted]	-	-	-
		TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABI, abiraterone; EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OLA, olaparib; QALYs, quality adjusted life years; rPFS, radiographic progression-free survival; SE, standard error; SRE, skeletal-related event; TALA, talazoparib; TTD, time to discontinuation; WTP willingness to pay

The model demonstrated some sensitivity to the assumption used for the effectiveness of abiraterone in the comparison to abiraterone monotherapy (Table 48). In threshold analysis the EAG could not find a hazard ratio in which talazoparib with enzalutamide was cost-effective in the comparison to abiraterone using list prices for treatments other than talazoparib.

Table 48: EAG's scenario analysis vs abiraterone

	Preferred assumption	Treatment	Total costs (£)	Total QALYs	Inc. costs	Inc. QALYs	ICER
6.2.9	Use OS and rPFS HR ABI vs ENZA from TA951 (1.19)	ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		TALA + ENZA					

Abbreviations: ABI, abiraterone; EAG, external assessment group; ENZA, enzalutamide; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OLA, olaparib; QALYs, quality adjusted life years; rPFS, radiographic progression-free survival; SE, standard error; SRE, skeletal-related event; TALA, talazoparib; TTD, time to discontinuation; WTP willingness to pay

6.5. Conclusions of the cost-effectiveness section

Results of the economic analysis for the comparison with olaparib with abiraterone indicated that the key drivers of cost-effectiveness were the assumptions made for TTD for olaparib with abiraterone and to a lesser extent the source of data used for post-progression utilities.

The company assumed the TTD is considerably lower than rPFS for talazoparib with enzalutamide resulting in a reduction in drug cost for talazoparib and enzalutamide of [redacted]. This bias came from two sources:

- Assumption that TTD = rPFS for olaparib with abiraterone and not talazoparib with enzalutamide which did not align with the prior NICE or CADTH appraisal for olaparib with abiraterone
- Use of unweighted data (rPFS was longer in the weighted dataset and therefore TTD would also be expected to be longer)

This resulted in a mean time on first line treatment of [redacted] months for talazoparib as part of the combination compared to [redacted] for olaparib. Given that rPFS is shorter for olaparib this did not appear plausible.

EAG scenario analysis demonstrated considerable model sensitivity to assumptions around TTD.

The post progression utilities used in the submitted company model were lower than those used in prior appraisals and prior models identified in a recent literature review. The assumption of lower utilities post progression benefits talazoparib with enzalutamide as this treatment increased the time spent progression-free and reduced the time spent post-progression.

In the comparison to monotherapy treatments the key drivers were the treatment cost used (as abiraterone is now generic and considerably cheaper than enzalutamide) and to a lesser extent the source of data used for post-progression utilities.

Remaining uncertainties which could not be addressed were:

- Inability to present a fully incremental analysis as the populations used in the preferred analysis for comparison with olaparib with abiraterone (MAIC weighted) differs to the population used in the comparison to enzalutamide (unweighted)
- The use of the MAIC weighted population provided more favourable life years gained (and QALYs) indicating that a comparison using the **TALAPRO-2** population would be likely to be less favourable in the comparison with olaparib with abiraterone
- Each of the ITCs submitted offered a different estimate of effect for the efficacy of talazoparib with enzalutamide versus olaparib with abiraterone for PFS and OS, and each had substantial uncertainty/flaws. The analysis was relatively sensitive to which estimate which used in part due to differences in relative effect but also due to the unweighted population providing less favourable estimates of absolute survival compared to the MAIC weighted population

The EAG also noted that the company did not supply cost-effectiveness analysis according to HRR subgroup as requested in the NICE scope. Clinical effectiveness results indicated that in comparison to enzalutamide greater effectiveness may be expected in people with HRR deficient tumours compared to the HRR non-deficient or unknown subgroup (see Section 3.2.3.2). The direction of impact on cost-effectiveness results was less clear as greater

effectiveness may be accompanied by a greater time on treatment. This increased uncertainty in the comparison to enzalutamide as clinicians have indicated they predominantly use both PARP inhibitors in HRR deficient patients; a subgroup for which results have not been presented.

7. QALY MODIFIER

The company did not ask for consideration of a severity modifer.

A 71-year-old male in the general population was expected to have remaining lifetime QALYs of 8.63. With mCRPC, this falls to 3.70 QALYs, resulting in an absolute shortfall of 4.93 QALYs and a proportional shortfall of 0.57. These estimates were obtained using the QALY Shortfall Calculator.[72] As the population has a proportional shortfall below 0.85 and an absolute shortfall below 12, the criteria for applying severity modifiers are not met. In accordance with NICE's methods guidance (Section 6.2), this case is therefore assigned a QALY weight of 1.

References

1. Asim M, Tarish F, Zecchini HI. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun. 2017;8:374.
2. NICE. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer: Final scope. 2024.
3. Ng KL. The Etiology of Prostate Cancer. In: Bott SRJ, Ng KL, editors. Prostate Cancer. Brisbane (AU): Exon Publications. Copyright: The Authors.; 2021.
4. Bashir MN. Epidemiology of Prostate Cancer. Asian Pac J Cancer Prev. 2015;16(13):5137-41.
5. Sung H, Ferlay J, Siegel RL. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-49.
6. Cancer Research UK. Prostate cancer statistics. Cancer Research UK. 2020.
7. 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.
8. Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019;10(2):63-89.
9. Morgan C, McEwan P, Chamberlain G, Cabrera C, Parry D. PCN17 CASTRATION-RESISTANT PROSTATE CANCER (CRPC): A UK EPIDEMIOLOGY STUDY. Value in Health. 2010;13(3):A26.
10. Shore N, Oliver L, Shui I. Systematic Literature Review of the Epidemiology of Advanced Prostate Cancer and Associated Homologous Recombination Repair Gene Alterations. J Urol. 2021;205:977-86.
11. Shore ND, Laliberté F, Ionescu-Ittu R, Yang L, Mahendran M, Lejeune D, et al. Real-World Treatment Patterns and Overall Survival of Patients with Metastatic Castration-Resistant Prostate Cancer in the US Prior to PARP Inhibitors. Adv Ther. 2021;38(8):4520-40.
12. NICE. Prostate cancer: diagnosis and management. NICE guideline NG131.; 2021.
13. Parker C, Castro E, Fizazi K. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:1119-34.
14. NICE. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer - Final draft guidance. 2023.
15. Choi E, Buie J, Camacho J, Sharma P, de Riese WTW. Evolution of Androgen Deprivation Therapy (ADT) and Its New Emerging Modalities in Prostate Cancer: An Update for Practicing Urologists, Clinicians and Medical Providers. Res Rep Urol. 2022;14:87-108.
16. Grossmann M, Cheung AS, Zajac JD. Androgens and prostate cancer; pathogenesis and deprivation therapy. Best Practice & Research Clinical Endocrinology & Metabolism. 2013;27(4):603-16.
17. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65(2):467-79.
18. NICE. NICE TA951: Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer. 2024.
19. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. 2016;375(5):443-53.
20. European Medicines Agency. Talzenna (Talazoparib) 2023. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/talzenna.
21. Peninsula Technology Assessment Group (PenTAG) UoEMS. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]: A Cost Comparison Appraisal. 2024.

22. Agarwal N, Azad AA, Carles J. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023;402:291-303.
23. Castro E, Ellis J, Craigie S, Haltner A, Nazari J, Niyazov A, et al. Comparative efficacy and safety of talazoparib plus enzalutamide and other first-line treatments for metastatic castration-resistant prostate cancer. Oncologist. 2024.
24. Castro E, Wang D, Walsh S, Craigie S, Haltner A, Nazari J, et al. Matching-adjusted indirect comparison of talazoparib plus enzalutamide versus abiraterone acetate and docetaxel in mCRPC. Future Oncol. 2025:1-10.
25. Clarke NW, Armstrong AJ, Oya M, Shore N, Procopio G, Daniel Guedes J, et al. Efficacy and Safety of Olaparib Plus Abiraterone Versus Placebo Plus Abiraterone in the First-line Treatment of Patients with Asymptomatic/Mildly Symptomatic and Symptomatic Metastatic Castration-resistant Prostate Cancer: Analyses from the Phase 3 PROpel Trial. Eur Urol Oncol. 2025;8(2):394-406.
26. Fizazi K, Azad AA, Matsubara N, Carles J, Fay AP, De Giorgi U, et al. Talazoparib plus enzalutamide versus placebo plus enzalutamide for patients with advanced prostate cancer and changes in specific DNA repair genes: a plain language summary of the results from the TALAPRO-2 study. Future Oncol. 2025;21(6):637-52.
27. Matsubara N, Miyake H, Uemura H, Mizokami A, Kikukawa H, Kosaka T, et al. Phase 3 Study of Talazoparib Plus Enzalutamide Versus Placebo Plus Enzalutamide as First-Line Treatment in Patients With Metastatic Castration-Resistant Prostate Cancer: TALAPRO-2 Japanese Subgroup Analysis. Cancer Med. 2025;14(1):e70333.
28. Narang A, Hage Chehade C, Ozay ZI, Nordblad B, Swami U, Agarwal N. Talazoparib for the treatment of prostate cancer. Expert Opin Pharmacother. 2024;25(13):1717-27.
29. Oya M, Joung JY, Lee JY, Sugimoto M, Choi YD, Hong JH, et al. Olaparib Plus Abiraterone in Asian Patients With Metastatic Castration-Resistant Prostate Cancer: PROpel Subset Analysis. Cancer Sci. 2025.
30. Qureshi Z, Fatima E, Safi A, Khanzada M, Altaf F. Talazoparib for the Treatment of Metastatic Castration-resistant Prostate Cancer: A Narrative Review. Am J Clin Oncol. 2025;48(4):206-14.
31. Roberto M, Di Civita MA, Marinelli D, Torchia A, Cara N, Maltese G, et al. PARP inhibitor-based treatment in metastatic, castration-resistant prostate cancer (mCRPC): A systematic review and meta-analysis. BJUI Compass. 2025;6(1):e455.
32. Saad F, Armstrong AJ, Oya M, Vianna K, Özgüroğlu M, Gedye C, et al. Tolerability of Olaparib Combined with Abiraterone in Patients with Metastatic Castration-resistant Prostate Cancer: Further Results from the Phase 3 PROpel Trial. Eur Urol Oncol. 2024;7(6):1394-402.
33. Serra R, Giunta EF, Schepisi G, Brighi N, Montanari D, Lolli C, et al. An evaluation of talazoparib plus enzalutamide for the treatment of metastatic castration-resistant prostate cancer. Expert Rev Anticancer Ther. 2024;24(12):1221-7.
34. Castro E, Wang D, Walsh S, Craigie S, Haltner A, Nazari J, et al. Talazoparib plus enzalutamide versus olaparib plus abiraterone acetate and niraparib plus abiraterone acetate for metastatic castration-resistant prostate cancer: a matching-adjusted indirect comparison. Prostate Cancer Prostatic Dis. 2024.
35. Azad AA, Fizazi K, Matsubara N, Saad F, De Giorgi U, Joung JY, et al. Talazoparib plus enzalutamide in metastatic castration-resistant prostate cancer: Safety analyses from the randomized, placebo-controlled, phase III TALAPRO-2 study. Eur J Cancer. 2024;213:115078.
36. Pfizer. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]. Addendum: Company evidence submission.; 2025.
37. Pfizer. TALAPRO 2 CSR. (Data on file). 2024.

38. S PDBJP. NICE DSU Technical Support Document 9: The Identification, Review and Synthesis of Health State Utility Values from the Literature. National Institute for Health and Care Excellence (NICE). 2010.
39. Agarwal N, Azad A, Carles J, Fay AP, Matsubara N, Szczylik C, et al. Final overall survival (OS) with talazoparib (TALA) + enzalutamide (ENZA) as first-line treatment in unselected patients with metastatic castration-resistant prostate cancer (mCRPC) in the phase 3 TALAPRO-2 trial. Journal of clinical oncology. 2025;43(5_suppl):LBA18-LBA.
40. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evidence. 2022;1(9):EVIDoa2200043.
41. Armstrong AJ, Lin P, Higano CS. Development and validation of a prognostic model for overall survival in chemotherapy-naïve men with metastatic castration-resistant prostate cancer. Annals of oncology. 2018;29:2200-7.
42. Phillippo D, Ades T, Dias S. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
43. Pfizer. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]: Document B, company evidence submission. 2024.
44. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evidence. 2022;1(9):EVIDoa2200043.
45. Duru E, Mattingly TJ, Malone DC. EE29 Cost-Effectiveness of Niraparib Plus Abiraterone Acetate and Prednisone for Metastatic Castration-Resistant Prostate Cancer. Value in Health. 2024;27(6):S62.
46. Zeng X, Liu Q, Tan C, Wan X, Wang Y, Ma X. Alpha emitter radium-223 in patients with metastatic castration-resistant prostate cancer: A cost-utility analysis. Front Pharmacol. 2022;13:1003483.
47. Goudarzi Z, Lotfi F, Najafpour Z, Hafezi A, Zakaria MA, Keshavarz K. Cost-effectiveness and budget impact analysis of enzalutamide in comparison to abiraterone in treatment of metastatic prostate cancer resistant to castration in Iran. BMC Urol. 2024;24(1).
48. Brockbank J, Hancock H, Khare A, Joshi P, Risson V. EE337 Cost-Effectiveness of [¹⁷⁷Lu]Lu-PSMA-617 in Progressive PSMA-Positive Metastatic Castration-Resistant Prostate Cancer. Value in Health. 2024;27(12):S121.
49. Fu J, Franzen N, Aas E, Koen van der Mijn JC, van Leeuwen PJ, Retel VP. Early Cost-Effectiveness Analysis of Using Whole-Genome Sequencing for Patients With Castration-Resistant Prostate Cancer. Value Health. 2025.
50. Barata P, Ribbands A, Montgomery R, Last M, Arondekar B, Ivanova J, et al. P067 - Health-related quality of life among men receiving treatment for metastatic castration-resistant prostate cancer: Results from an international real-world study. European Urology Open Science. 2022;45:S136.
51. Castro E, Figliuzzi R, Walsh S, Craigie S, Nazari J, Niyazov A, et al. Systematic literature review and meta-analysis of health state utility values in metastatic castration-resistant prostate cancer. Oncologist. 2024:oyae321.
52. Wolff J, Tolle A, Gedamke M. Health care cost in hormone-naive and hormonally pretreated patients with prostate cancer treated with degarelix. Journal of clinical oncology. 2012;30(5_suppl):240-.
53. Diels J, Hamberg P, Ford D, Price PW, M S. Mapping FACT-P to EQ-5D in a large cross-sectional study of metastatic castration-resistant prostate cancer patients. Quality of Life Research. 2015;24(3):591-8.
54. NICE. NICE health technology evaluations: the manual. 2023.
55. CADTH Reimbursement Reviews and Recommendations. Olaparib (Lynparza): CADTH Reimbursement Recommendation: Indication: In combination with abiraterone and prednisone

or prednisolone for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic BRCA-mutated metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated BRCA mutation must be confirmed before olaparib treatment is initiated. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2024.
56. Leith A, Ribbands A, Kim J, Clayton E, Gillespie-Akar L, Yang L, et al. Impact of next-generation hormonal agents on treatment patterns among patients with metastatic hormone-sensitive prostate cancer: a real-world study from the United States, five European countries and Japan. BMC Urol. 2022;22(1):33.
57. Tannock IF, Wit R, Berry WR. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502-12.
58. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019;381(26):2506-18.
59. Pemberton L, Allen C, Handel E. Carboplatin in Metastatic Castrate Resistant Prostate Cancer: A Retrospective Study of Heavily Pretreated Patients (COMPACT. Clin Genitourin Cancer. 2024;22:580-5.
60. EMC. Xofigo 1100 kBq/mL solution for injection SmPC. 2024.
61. NICE. User guide for the cost comparison company evidence submission template. 2022.
62. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics. 2023;41(2):199-207.
63. NICE. TA951. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer 2024. Available from: https://www.nice.org.uk/guidance/ta951/resources/olaparib-with-abiraterone-for-untreated-hormonerelapsed-metastatic-prostate-cancer-pdf-82615723963333.
64. Drugs and pharmaceutical electronic market information tool (eMIT). GOV.UK 2024. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
65. Fierce Pharma. The top 15 blockbuster patent expirations coming this decade 2021. Available from: https://www.fiercepharma.com/special-report/top-15-blockbuster-patent-expirations-coming-decade.
66. European Medicines Agency. Enzalutamide Viatris 2024. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/enzalutamide-viatris.
67. NHS. NHS Electronic Drug Tariff 2025. Available from: https://www.drugtariff.nhsbsa.nhs.uk/#/00885392-DC/DC00885322/Part%20IIIA%20-%20Professional%20Fees%20(Pharmacy%20Contractors).
68. EMA. Talzenna SmPC. 2024.
69. EMC. Xtandi SmPC. 2024.
70. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. Eur J Cancer Care (Engl). 2006;15(1):65-73.
71. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. Palliat Med. 2015;29(10):899-907.
72. Schneider PM, S. Love-Koh, J. Doran, T. Gutacker, N. QALY Shortfall Calculator. 2021. Available from: https://shiny.york.ac.uk/shortfall.

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

A Cost Comparison Appraisal

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

Term	*Definition*
ADT	Androgen deprivation therapy
AE	adverse event
AR	Androgen receptor
ARPi	androgen receptor pathway inhibitors
ATX	Ataxia-telangiectasia mutated
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CRPC	castration-resistant prostate cancer
CS	company submission
CT	Computed tomography
CTC	Circulating tumour cells
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EAG	External Assessment Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire
EORTC QLQ-PR25	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Prostate 25
EQ-5D-5L	EuroQol five dimension (five level)
FACT-P	Functional Assessment of Cancer Therapy Prostate Cancer
HRQoL	health-related quality of life
HRR	Homologous recombination repair
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ITT	Intention-to-treat
mCRPC	Metastatic castration-resistant prostate cancer
MHRA	Medicines and Healthcare products Regulatory Agency
NA	not applicable
NHA	Novel hormonal agent

Term	*Definition*
NHS	National Health Service
NHT	Novel hormonal therapy
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
nmCRPC	Non-metastatic castration-resistant prostate cancer
NR	not reported
ORR	Objective response rate
OS	Overall survival
OWSA	one-way sensitivity analysis
PARP	Poly ADP ribose polymerases
PAS	Patient-access scheme
PFS2	time to second progression or death
PRO	patient reported outcomes
PSA	prostate-specific antigen
QA	quality assessment
QALY	quality adjusted life year
RCT	randomised controlled trial
rPFS	radiographic progression-free survival
SD	standard deviation
SLR	systematic literature review
TA	Technology Appraisal
TFST	time to first subsequent anticancer therapy or death
vs	Versus
WTP	willingness to pay

1. SUMMARY OF THE EAG'S VIEW OF THE COMPANY'S COST COMPARISON CASE

1.1. Similarity of effectiveness of talazoparib with enzalutamide relative to olaparib with abiraterone

The company did not robustly demonstrate similarity of effectiveness of talazoparib with enzalutamide relative to olaparib with abiraterone in adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated.

The company conducted the NMA by using a Cox proportional hazards model within a Bayesian framework. However, the proportional hazards (PH) assumption was implausible for the radiological progression free survival (rPFS) and overall survival (OS) NMAs (Section 3.5.5.4). Violating the PH assumption can lead to biased estimates and inaccurate conclusions, and thus, the EAG did not consider the results of the NMA to be robust.

However, based on the flawed NMA presented, the EAG's preferred FE model for rPFS [redacted] and found talazoparib with enzalutamide [redacted] olaparib with abiraterone (Sections 3.5.6. and 3.5.7.1). All the models presented in the CS were consistent for OS and found [redacted] to be [redacted].

1.2. Safety of the treatment

Talazoparib with enzalutamide demonstrated increased toxicity compared to olaparib with abiraterone on the basis of a naïve comparison between the intervention arms in the TALAPRO-2 and PROpel trials (Section 3.4.3). Permanent drug discontinuation due to adverse events (AEs) was higher for talazoparib (18.8%) than olaparib (13.8%), and Grade ≥3 adverse events were experienced by 75.1% of participants in the talazoparib with enzalutamide arm and 47.2% of people in the olaparib with abiraterone arm. The EAG caution that there were differences in the populations recruited to each trial but considered this moderate evidence that talazoparib with enzalutamide has higher toxicity than olaparib with abiraterone.

1.3. Similarity of costs across interventions

As noted in Section 1.1, [redacted]

[redacted]. Under similarity of effect, the company made the assumption that the two combination therapies have the same treatment lengths which may not hold (section 5.1.2). Furthermore, the use of rPFS as a proxy to treatment duration may bias the results as the correlation between rPFS and treatment duration may be weak (see Table 18). Less importantly, the EAG preferred to equalize the monitoring incidences for both treatments as opposed to the company base case that included a reduced monitoring requirement for talazoparib with enzalutamide as clinical feedback on the realism of reduced monitoring costs was mixed (section 4.1.3). The economic implications of the EAG and company analysis are not presented in this report as all four treatments have confidential discounts in place; these can be found in the cPAS appendix. Overall, however, the cost comparison approach to appraise talazoparib with enzalutamide vs. olaparib with abiraterone is not considered appropriate as the evidence [redacted] leading to increased intervention costs.

1.4. Areas of uncertainty

In relation to the clinical data, the EAG noted four areas of uncertainty:

1. The PH assumption was implausible for the rPFS or OS NMAs. Violating the PH assumption can lead to biased estimates and inaccurate conclusions, and the the Cox proportional hazards model should be replaced an analysis more suited to the available evidence, such as an unanchored matching-adjusted indirect comparison (MAIC) based method or fractional polynomials.
2. The best fitting model (by deviance information criterion) for rPFS in the CS was the FE model. The FE model found talazoparib with enzalutamide [redacted] olaparib with abiraterone for rPFS. Therefore, it was not appropriate to make an assumption of [redacted] in rPFS between the treatments.
3. The naïve comparison of safety between the TALAPRO 2 and PROpel trials finds moderate evidence that talazoparib with enzalutamide has higher toxicity than olaparib with abiraterone. Therefore, it was not appropriate to make an assumption of similarity of safety between the treatments.
4. The NMA, independent of which model was used, found enzalutamide monotherapy to [redacted] olaparib with abiraterone for rPFS, and [redacted] for OS. Given this result, it may not have been appropriate to exclude enzalutamide monotherapy as a comparator for this appraisal.

In relation to the HE analysis, the main uncertainty stemmed from the assumption of comparable efficacy that led to the exclusion from the analysis of HRQoL and subsequent treatment costs (e.g. CEA). The EAG did not agree with the approach to costs in the model as two TTD curves were expected for each comparison arm and that would constitute the best approach to handle costs. Instead, the company assumed that all treatments have the same treatment duration and that it is equal to talazoparib with enzalutamide rPFS.

2. CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The company submission (CS) assessed the clinical and cost effectiveness of talazoparib with enzalutamide for the treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated, within the technology's full marketing authorization[1]. A summary of the decision problem for this appraisal, and the EAG's critique of how the CS addresses it, is shown in Table 1 below.

2.1. Population

The population recruited to TALAPRO-2 were adults with mCRPC who were asymptomatic or mildly symptomatic. The final scope issued by NICE[2] also required the adults were not clinically indicated for chemotherapy (docetaxel). The company clarified that adults were not eligible for chemotherapy for three reasons and the EAG have related the three reasons to the participants in the TALAPRO-2 trial below:

1. They may have previously received docetaxel treatment for mCRPC and re-treatment for mCRPC was not permitted.

An exclusion criterium in TALAPRO-2 was any prior systematic cancer treatment, such as docetaxel, initiated in the nonmetastatic castration-resistant prostate cancer (nmCRPC) or mCRPC disease state. While 22.2% of participants in the trial had received docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC), the company clarified (response A1) that they would be permitted to receive docetaxel for mCRPC. Thus, no participants in the trial were prevented from receiving docetaxel for mCRPC due to previous docetaxel treatment.

2. They were not fit enough to receive docetaxel.

In clarification response A1, the company stated that clinicians would consider various factors when determining eligibility for docetaxel, including performance status, severity of symptoms, and patient preferences. The EAG's clinical experts stated that their practices used Eastern Cooperative Oncology Group (ECOG) performance status score. A person with a score of 0-2 was suitable for chemotherapy, though a score of 0-1 was preferred. An ECOG score of 0-1 was an inclusion criterium for the TALAPRO-2 trial and therefore, by that standard, all the people recruited to the trial were fit enough to receive docetaxel treatment.

3. Docetaxel may be contraindicated for them.

The company expanded on the contraindications for docetaxel at the clarification stage (response A1). They explained that in the summary of product characteristics (SmPC)[3], contraindications included people with hypersensitivity to the active substance or the excipients, baseline neutrophil count of <1,500 cells/mm, or severe liver impairment. However, people with liver function abnormalities, and people with low neutrophil counts, were excluded from the TALAPRO-2 trial.

Therefore, the EAG consider the TALAPRO-2 participants for the most part to be clinically indicated for chemotherapy. However, the EAG recognised that patient choice was important in the initial therapy people received. The participants in TALAPRO-2 may be categorised as adults who did not choose chemotherapy and instead chose enzalutamide monotherapy or talazoparib with enzalutamide.

2.2. Intervention and comparator

The intervention and comparator assessed were in line with the final scope issued by NICE. Olaparib with abiraterone was found to be cost effective compared to both enzalutamide monotherapy and abiraterone (with prednisone or prednisolone) in TA951[4]. The company reasoned that if talazoparib with enzalutamide had similar effectiveness, safety and cost as olaparib with abiraterone, then given the prior decision by NICE, it would also be cost effective versus enzalutamide monotherapy and abiraterone (with prednisone or prednisolone). This allowed the company to use the cost comparison approach for this appraisal. Abiraterone (with prednisone or prednisolone) will henceforth be referred to as abiraterone monotherapy or abiraterone in this report.

The company noted the similarity of the treatments between the intervention and comparator. Talazoparib and olaparib are both poly adenosine diphosphate ribose polymerase (PARP) inhibitors. Both medications block the action of an enzyme called human poly ADP ribose polymerase, which helps to repair damaged DNA in normal and cancer cells during cell division. When PARP is blocked, the damaged DNA in cancer cells cannot be repaired and, as a result, the cancer cells die. Cancer cells with homologous recombination repair (HRR) deficiency, such as the BRCA1 or BRCA2 mutations, rely more heavily on PARP to repair their DNA and continue dividing. Therefore, PARP inhibitors are understood to be more effective in cancer cells that have homologous recombination repair (HRR) deficiency.

Androgen receptor pathway inhibitors (ARPis), such as enzalutamide or abiraterone, work by reducing the levels of androgens in people. Androgens, including testosterone, are necessary for prostate cancers to grow. People with mCRPC have either been surgically or chemically castrated, and this reduces the level of androgen in the blood by as much as 95%. The remaining androgen can be addressed using ARPis and this further reduces the androgens present in the body after castration. While enzalutamide and abiraterone are both ARPis and the overall effect is similar, they have different mechanisms of action and different safety profiles. Enzalutamide works by blocking the action of the male hormone testosterone and other male hormones (androgens). It does this by blocking the receptors to which those hormones attach. Abiraterone works by stopping the body from producing testosterone by blocking an enzyme called CYP17 found in the testes and elsewhere in the body. Abiraterone is taken with oral prednisone to help manage side effects that might occur. The EAG noted that ARPis are also called novel hormonal therapies (NHTs) and novel hormonal agents (NHAs) in the CS.

2.3. Outcomes

Each of the outcomes in the final scope issued by NICE was presented for the TALAPRO-2 trial. The NMA presented in the CS evaluated three of the outcomes detailed in the final scope issued by NICE: overall survival, progression-free survival, and response rate. However, the NMA did not evaluate adverse effects of treatment or health-related quality of life.

2.4. Subgroups

The final scope issued by NICE requested subgroup analysis using participant's HRR status. The EAG understood this was included because PARP inhibitors, such as talazoparib and olaparib, had increased efficacy against tumors with HRR deficiency. However, the company stated that in line with NICE guidance on cost comparisons, results of subgroup analyses were not required if the technology provides similar or better health benefits at a similar or lower price than the intervention in the full population. Therefore, no such analysis was planned. Also, in Table 2 of the CS, the company noted the proposed synergistic effect when PARP inhibitors and ARPis such as enzalutamide and abiraterone, are used in combination. Research undertaken by Asim et al. (2017)[5] suggested that androgen deprivation therapy (ADT), including ARPis, could functionally impair HRR and this could potentially be exploited therapeutically by using combination therapy with PARP inhibitors.

However, despite the proposed synergistic effect but in line with the understanding that PARP inhibitors are effective against tumors with HRR deficiency, the EAG's clinical experts stated

that it was unlikely PARP inhibitors would be offered to people with HRR non-deficient tumours in their practices.

Table 1: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated	In line with scope	N/A	Based on input for their clinical experts and the company's clarification response (A1), the EAG considered the participants of the TALAPRO-2 trial to be clinically indicated for chemotherapy. The participants in TALAPRO-2 may be categorised as adults who did not choose chemotherapy and instead chose ARPi or ARPi with PARP inhibitor therapy.
Intervention	Talazoparib in combination with enzalutamide	In line with scope	N/A	Appropriate
Comparator(s)	~~• Enzalutamide~~ ~~• Abiraterone with prednisone or prednisolone~~ • Olaparib with abiraterone (and prednisone or prednisolone)	Olaparib with abiraterone	Olaparib with abiraterone represents the only relevant comparator for this cost comparison submission. Although enzalutamide monotherapy and abiraterone monotherapy are also in the same position in the treatment pathway as talazoparib with enzalutamide and olaparib with abiraterone, they are not relevant to this cost comparison appraisal because olaparib with abiraterone was shown to be cost-effective against both	The EAG have crossed out the monotherapy comparators detailed in Table 1 in the CS as they do not appear in the final scope issued by NICE.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
			enzalutamide monotherapy and abiraterone monotherapy in TA951. Given that talazoparib with enzalutamide provides similar or greater health benefits at similar or lower costs than olaparib with abiraterone, a comparison versus enzalutamide and abiraterone is therefore not required.	
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	In line with scope	N/A	Each of these outcomes was presented for the TALAPRO-2 trial. The NMA evaluated overall survival, progression-free survival, and response rate for the talazoparib with enzalutamide versus olaparib with abiraterone comparison. However, the NMA did not evaluate adverse effects of treatment or health-related quality of life.
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	In line with scope	This submission presents a cost comparison of talazoparib with enzalutamide versus olaparib with abiraterone (see Section B.4 of the CS for details). As talazoparib with enzalutamide is licensed for all eligible adult patients with mCRPC in whom chemotherapy is not clinically indicated, regardless of biomarker	The EAG agrees with the approach if comparable efficacy is demonstrated

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	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. The economic modelling should include the cost associated with diagnostic testing for people with hormone-relapsed metastatic prostate cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		status, no specific genetic testing is required. There will be no further monitoring requirements beyond current clinical practice.	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment

Subgroups	If the evidence allows, the following subgroups should be considered:
	• HRR status including:
	  ○ BRCA1 and BRCA2
	  ○ ATM gene.
		None	According to NICE guidance on cost comparisons, results of subgroup analyses are not required if the technology provides similar or better health benefits at a similar or lower price than the intervention in the full population. As this is the case for the comparison of talazoparib with enzalutamide versus olaparib with abiraterone, subgroup analyses are not presented.	The EAG received advice from their clinical experts that UK practices may not offer PARP inhibitor treatment to people who are HRR non-deficient. At the clarification stage, the company undertook cost-minimisation analysis using efficacy data from the HRR non-deficient subgroup to support use of talazoparib with enzalutamide in that population.

Special considerations including issues related to equity or equality	Not presented	Not presented	N/A	None

Abbreviations: ARPI, androgen receptor pathway inhibitors ATM, Ataxia-telangiectasia mutated; BRCA, Breast cancer susceptibility gene; CS, company submission; EAG, external assessment group; HRR, Homologous recombination repair; mCRPC, Metastatic castration-resistant prostate cancer; N/A, Not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PARP, Poly ADP ribose polymerases; TA, Technology appraisal.

3. SUMMARY OF THE EAG'S CRITIQUE OF THE CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

3.1. Systematic literature review conducted by the company

3.1.1. Clinical systematic literature review

The company undertook a clinical systematic literature review (SLR) to identify clinical trials evaluating treatments for people with metastatic castration-resistant prostate cancer (mCRPC) who were asymptomatic or mildly symptomatic in the first-line setting. The SLR was undertaken to find relevant studies for the network meta-analysis (NMA). An overview of the SLR methods used by the company and the EAG appraisal of these is shown in Table 2.

The inclusion criteria and screening process appeared to be appropriate. The EAG checked the RCTs excluded from the search were correctly excluded given the planned NMA. The EAG noted one trial that appeared to be inappropriately excluded. The NCT02125357 crossover trial compared enzalutamide monotherapy to abiraterone monotherapy with participants crossing over after disease progression. In table 15 of Appendix J of the CS, the company noted that the trial had relevant outcomes, such as rPFS, which occurred prior to treatment crossover. The EAG was concerned that the company did not offer a transparent reasoning why RCTs in the correct population, such as NCT02125357, were not used in the NMA. However, the company later acknowledged this was a typographical error in the CS and that the NCT02125357 trial did not report rPFS.

The company used the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs on the NICE website[6] to assess the studies included in the NMA. There were limitations to the risk of bias assessment presented in Table 12 in Appendix D of the CS. The company answered yes/no/not clear to each of the seven criteria but offered no reasoning for this assessment. In addition, no overall risk-of-bias judgement was made for each study. Given these limitations it was not clear from the assessment presented how the risk of bias in included studies caused by inadequacies in study design, conduct or analysis may have led to the treatment effect being over or underestimated.

The company conducted an NMA to indirectly compare talazoparib with enzalutamide to olaparib with abiraterone. The EAG's critique of the methods of the NMA are presented in Section 3.5.4.

Table 2: Summary of EAG's critique of the methods implemented by the company to identify clinical evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D 1.1	Searches were well conducted on the whole, with a good selection of both databases and grey literature sources used. A good range of keywords and subject headings were selected. The searches excluded children by combining the search results with 'NOT children' (see for example Table 1 lines 74-76 of the Embase search strategy). This is a risky approach that may have resulted in some relevant papers being excluded (if a paper mentioned 'children' in the abstract but this was not the main subject of the paper, it would have been excluded from the search results).
Inclusion criteria	Appendix D1.2, Table 5	The inclusion criteria appear to be appropriate. Under timeframe it was stated that "Publications published prior to November 14, 2023" would be excluded. However, this appeared to be a typographical error as studies published prior to this date were included.
Screening	Appendix D.1.2	The criteria were appropriate.
Data extraction	Appendix D.1.2	Appropriate
Tool for quality assessment of included study or studies	Appendix D2.3	The company undertook the minimum required to assess risk of bias for the studies in the NMA, and there were limitations in the implementation and reporting of the assessment. Given these limitations it was not clear from the assessment presented how the risk of bias in included studies caused by inadequacies in study design, conduct or analysis may have led to the treatment effect being over or underestimated.
Evidence synthesis	B3.9	The company conducted an NMA to indirectly compare talazoparib with enzalutamide to olaparib with abiraterone. The EAG critique of the

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
		methods of the NMA are presented in Section 3.5.4.

Abbreviations: CS, Company submission; EAG, External Assessment Group; NMA, network meta-analysis; NICE, National Institute for Health and Care Excellence.

3.1.2. Healthcare resource use systematic literature review

The company conducted a systematic review of healthcare resource use which is presented in Appendix G. This is not, however, used to inform the cost comparison analysis presented (the Appendix is not referenced in the CS). The appraisal used by the company to inform their approach to the cost comparison analysis (TA951) was not identified in the systematic review as the searches were last updated in October 2022. The EAG do, however, agree with this being the most relevant appraisal to use as a starting point for healthcare resource use assumptions.

3.2. Overview of clinical evidence submitted by the company

The submission comprised one pivotal trial (TALAPRO-2[7]) of talazoparib with enzalutamide versus placebo with enzalutamide. Seven further trials were used in the NMA, including the PROpel trial[8], which compared olaparib with abiraterone to placebo with abiraterone.

3.3. Methodology of pivotal trial

An overview of the methods used in the pivotal trial for talazoparib with enzalutamide (TALAPRO-2) is presented in Table 3. TALAPRO-2 recruited men with mCRPC with progressive disease and an ECOG performance status of 0 or 1. Participants were not permitted to have had prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state. Randomisation was stratified by homologous recombination repair (HRR) gene alteration status (deficient vs non-deficient or unknown), and they undertook subgroup analysis in people based on their tumour's HRR status. The EAG's clinical experts considered the methods, including the outcomes measured, to be appropriate and in line with other trials in this disease area.

Table 3: Summary of trial methodology

Study	TALAPRO-2: NCT03395197[7]
Location	287 sites in 26 countries in North America, Europe (including UK), Israel, South America, South Africa, and Asia-Pacific region.
Trial design	Randomised, double-blind, placebo-controlled, Phase 3 study
Number of participants	N=805 (cohort 1[a])

Study	TALAPRO-2: NCT03395197[7]
Eligibility criteria	- Adults with histologically/cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features. - Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan; - Surgically or medically castrated, with serum testosterone ≤50 ng/dL at screening; - Progressive disease at study entry in the setting of medical or surgical castration; - ECOG performance status ≤1; - Life expectancy ≥12 months as assessed by the investigator.
Exclusion criteria	- Any prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state. (ADT and first-generation anti-androgens received in the CRPC disease state were **not** exclusionary); - Prior docetaxel for mCSPC was allowed if more than 4 weeks had elapsed from the last dose of docetaxel.
Interventions evaluated	Talazoparib (0.5 mg/day) + enzalutamide (160mg/day) vs Placebo + enzalutamide (160mg/day)
Concomitant medication	Prohibited: prednisone >10 mg once daily, cytotoxic chemotherapy, hormonal therapy, other PARP inhibitor, NHT (with the exception of enzalutamide), biological therapy, radionucleotide therapy for prostate cancer, or investigative agents. Permitted: bisphosphonates or denosumab, ADT, hematopoietic growth factors, ESAs or RBC transfusions.
Primary outcomes	BICR-assessed rPFS or death
Key secondary outcomes	- Overall survival (OS) - Investigator-assessed rPFS - Overall response rate (ORR) - PSA response - Time to confirmed PSA progression - Quality of life using EQ-5D-5L - Cancer-specific global health status/QoL, functional scales, and symptom scales (EORTC-QLQ-C30) - Adverse events
Selected pre-planned subgroups	- HRR status (HRR deficient and HRR non-deficient / unknown) - Renal impairment (moderate, mild, normal) - Race (Asian, White, African American, other) - Prior NHT/ARPi (yes, no) - Prior docetaxel (yes, no)

Abbreviations: ADT, androgen deprivation therapy; ARPi, androgen receptor pathway inhibitor; BICR, blinded independent central review; CRPC, castration-resistant prostate cancer; CT, computed tomography scan; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol five dimension (five level) ; EORTC-QLQ-C30 European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; ESAs, erythropoietin Stimulating Agents; HRR, homologous recombination repair; ibPFS, imaging-based progression-free survival; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; ng/dL, nanograms per deciliter; NHT, novel

hormonal therapies; ORR, overall response rate; PARP, Poly ADP ribose polymerases; PSA, prostate specific antigen; rPFS, Radiographic progression-free survival; QoL, quality of life; RBC, red blood cells.

Note: [a] Cohort 1 were recruited to the trial and were not selected based on their HRR status.

3.3.1. Baseline characteristics

The company presented the baseline demographics and disease characteristics of the participants in the TALAPRO-2 trial in Table 6 in Document B. The EAG's clinical experts commented that the trial population was a reasonable reflection of the populations they see in their practice. One expert noted that the population in the trial may be slightly younger than the population he sees in his practice, but he did not consider this difference to be a significant treatment effect modifier that would benefit either arm.

3.3.2. Outcomes

The relevant outcomes collected in the trial were:

- Blinded independent central review rPFS: per RECIST 1.1 criteria for soft tissue and the PCWG-3 criteria for bone;
- Overall survival (OS): time from randomisation to death from any cause;
- Objective response rate (ORR): people with measurable soft tissue disease at baseline per RECIST 1.1);
- Prostate-specific antigen (PSA) response: 50% or greater;
- Time to confirmed PSA progression;
- Quality of life using EQ-5D-5L;
- Adverse events: including Grade ≥3 treatment emergent adverse events (TEAEs).

The trial also collected cancer-specific global health status/QoL, functional scales, and symptom scales (EORTC-QLQ-C30).

3.3.3. Dropouts

The disposition of people in the TALAPRO-2 trial was presented in Figure 2 in Document B of the CS and the EAG has adapted it in Table 4, below. Relatively few people (~8%) withdrew consent or were lost to follow-up during the study in each treatment arm. The company state (Table 8, Doc B) that missing data were not imputed, except for date of birth (if year of birth is available), date of last dose of study treatment, death date, date of start of follow-up cancer therapy, and adverse events. Given the low rate of missing data, the EAG consider this to be a reasonable approach. Discontinuations in Table 4 were reported for

each treatment, i.e. discontinuations were reported separately for talazoparib and for enzalutamide in the talazoparib with enzalutamide treatment arm. Therefore, it was not clear how many people discontinued both treatments, and whether they were discontinued at the same time.

Overall, discontinuations were higher for placebo (69.8%) than talazoparib (61.6%). This difference was due to higher disease progression (30.7% versus 19.1%) and lack of benefit (5.2% versus 3.5%). However, a higher proportion of people discontinued talazoparib than placebo due to adverse events (17.3% versus 10.7%) indicating higher toxicity of the combination therapy.

Discontinuations of enzalutamide were higher in the placebo with enzalutamide arm (68.8%) than the talazoparib with enzalutamide arm (57.0%). Again, this was primarily due to disease progression and lack of benefit. Discontinuations of enzalutamide due to adverse events, death, and global deterioration of health were close to identical between the two treatment arms.

Relatively few people (~8%) withdrew consent or were lost to follow-up during the study in each treatment arm. The company state (Table 8, Doc B) that missing data were not imputed, except for date of birth (if year of birth is available), date of last dose of study treatment, death date, date of start of follow-up cancer therapy, and adverse events. Given the low rate of missing data, the EAG consider this to be a reasonable approach.

Table 4: TALAPRO-2: participant disposition (adapted from Figure 2 in Document B)

	Talazoparib with enzalutamide (n=398)		**Placebo with enzalutamide (n=401)**	
n (%)	Talazoparib	Enzalutamide	Placebo	Enzalutamide
Total discontinued	245 (61.6)	227 (57.0)	280 (69.8)	276 (68.8)
Adverse events	69 (17.3)	37 (9.3)	43 (10.7)	36 (9.0)
Death	8 (2.0)	8 (2.0)	10 (2.5)	11 (2.7)
Lost of follow up	0	0	1 (0.25)	1 (0.25)
Disease progression	76 (19.1)	84 (21.1)	123 (30.7)	123 (30.7)
Withdrew consent	29 (7.3)	30 (7.5)	30 (7.5)	31 (7.7)
Global deterioration of health	44 (11.1)	48 (12.1)	46 (11.5)	47 (11.7)
Lack of benefit	14 (3.5)	15 (3.8)	21 (5.2)	22 (5.5)
Other reason	5 (1.3)	5 (1.3)	6 (1.5)	5 (1.2)

3.3.4. Critical appraisal

The company presented a critical appraisal of TALAPRO-2 in Section B.3.5 of the CS using the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs on the NICE website[6]. In contrast to the critical appraisal of the studies in the NMA, the company did offer reasoning for their judgements made for each risk of bias criteria. Again, no overall risk-of-bias judgement was stated but given the study was assessed to be at a low risk of bias for each criterium it is appropriate to conclude that the company judged TALAPRO-2 to be at low risk of bias overall. While the EAG agreed that TALAPRO-2 was a well conducted trial, the EAG had some concerns on the reporting of patient reported outcomes. It was unclear why the company only presented a key quality of life outcome, change in EQ-5D-5L index scores, as a graph. It would have been appropriate to present point estimates for the change in EQ-5D-5L index scores after 1 and 2 years of treatment to allow a fuller critique of the results.

3.4. Talazoparib with enzalutamide versus placebo with enzalutamide

3.4.1. Efficacy outcomes

The company presented evidence for Cohort 1 of the TALAPRO-2 trial in Section 3.6 in Document B. Cohort 1 comprised of what the company term the *all-comers* population i.e. participants were recruited to TALAPRO-2 irrespective of HRR gene alterations. The baseline demographics of the Cohort 1 participants were presented in Table 6 in Document B of the CS.

Selected results from the TALAPRO-2 trial are presented in Table 5, below. These were based on the pre-planned, final data cut-off date of August 16th 2022 (median follow-up for the primary analysis: 24.9 months for the talazoparib arm, 24.6 months for the placebo arm). Time-to-event endpoints were compared between treatment arms using a stratified log-rank test. HRs and associated two-sided 95% CIs were estimated by a Cox proportional hazards model. Median time-to-event endpoints were estimated by the Kaplan-Meier method, and 95% CIs were based on the Brookmeyer-Crowley method.

Talazoparib with enzalutamide demonstrated a clinically important increase in radiographic progression-free survival (rPFS) over placebo with enzalutamide (HR 0.63; 95% CI: 0.51 to 0.78, p<0.0001). Talazoparib with enzalutamide also had a statistically significant benefit over placebo with enzalutamide for time to PSA progression and time to PFS2. PFS2 was progression-free survival on next line therapy. However, both talazoparib with enzalutamide and placebo with enzalutamide were similarly effective for overall survival (OS) and time to

first symptomatic skeletal event. The company also presented best overall response, duration of response, time to initiation of cytotoxic chemotherapy, and time to initiation of subsequent antineoplastic therapy.

Table 5: Efficacy results from the TALAPRO-2 trial

	Talazoparib with enzalutamide (n=402)	**Placebo with enzalutamide (n=403)**	**Hazard ratio (95% CI)**	**2-sided p-value**
Median rPFS by BICR, months (95% CI)[a]	NR (27.5, NR) Events: 151 (37.6%)	21.9 (16.6, 25.1) Events: 191 (47.4%)	0.63 (0.51, 0.78)	<0.0001
Median[a] OS (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]
Objective response[b], n (%; 95% CI)	74 (61.6; 52.4, 70.4)	58 (43.9; 35.3, 52.8)	-	0.0050
PSA response ≥50%[c], n (%; 95% CI)	331 (83.6; 79.6-87.1)	284 (72.1; 67.4-76.5)	-	0.0001
Median time to PSA progression (95% CI), months	26.7 (21.2, 30.4)	17.5 (14.1, 20.8)	0.72 (0.58, 0.89)	0.0020
Median time to first symptomatic skeletal event (95% CI), months	NR (NR) Events: 91 (22.6%)	NR (NR) Events: 93 (23%)	0.88 (0.66, 1.18)	0.41
Median PFS2[d] (95% CI), months	36.4 (33.5, NR) Events: 126 (31.3%)	35.3 (28.6, NR) Events: 143 (35.5%)	0.77 (0.61, 0.98)	0.036

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CS, company submission; NMA, network meta-analysis; NR, not reported; OS, overall survival; PFS2, time from randomization to progression on second-line therapy; PSA, prostate specific antigen; RCT, randomised controlled trial.

Notes: [a] Based on the Brookmeyer-Crowley method; [b] Only includes patients with measurable soft tissue disease at baseline per BICR: talazoparib arm (n=120); placebo arm (n=132); [c] Only includes patients with a baseline PSA value and at least one post-baseline PSA value: talazoparib arm (n=396); placebo arm (n=394); [d] PFS2 based on investigator assessment (time from randomisation to the date of documented progression on the first subsequent antineoplastic therapy or death from any cause, whichever occurs first).

3.4.1.1. Subgroup analysis

As noted in Section 2, PARP inhibitors such as talazoparib and olaparib, are known to be more effective in tumour cells that are homologous recombination repair (HRR) deficient and the NICE final scope stated that if the evidence allows, the HRR status subgroup should be considered. Given the EAG's clinical experts stated that they would not offer a PARP

inhibitor to people who were HRR non-deficient, the EAG considered this subgroup analysis to be pertinent to this appraisal and could influence the uptake of the treatment within the NHS. Subgroup analysis was not presented in the CS, but it was presented in Agarwal et al. 2023.[7] The HRR status subgroup (as per randomisation stratification) analysis using the primary outcome (rPFS) found:

- HRR deficient (n=169): HR: 0·46; 95% CI 0·30, 0·70; p=0.0003.
- HRR non-deficient or unknown (n=636): HR: 0·70; 95% CI 0·54, 0·89; p=0.0039.
- All people (n=805): HR 0.63; 95% CI: 0.51, 0.78, p<0.0001).

Talazoparib with enzalutamide had a statistically significant benefit over placebo with enzalutamide in people whose tumours were HRR deficient and people whose tumours were HRR non-deficient or unknown. However, a tumour's HRR status was a large treatment effect modifier because the efficacy was reduced in people with HRR non-deficient or unknown tumours. At the clarification stage the company undertook cost-minimisation analysis using efficacy data from the HRR non-deficient/unknown subgroup to support use of talazoparib with enzalutamide in that population.

3.4.2. Patient reported outcomes

Overall QoL was measured using EuroQol-5 dimensions-5 levels (EQ-5D-5L) and this was presented as a plot (Figure 1) rather than change score. The graph appeared to show [redacted]. However, the EAG maintain that it would have been appropriate to present the mean difference with standard deviation for the change in EQ-5D-5L from baseline until discontinuation of treatment during the trial.

The company also collected prostate cancer-specific QoL, as measured by EORTC-QLQ-PR25. Again, no point estimates were presented but the company stated that there was [redacted] across all functional and symptom scales, with [redacted] between the treatment arms.

Overall cancer-related QoL, as measured by EORTC-QLQ-C30, [redacted] functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) [redacted]. However, there were EORTC-QLQ-C30 symptom scales, with [redacted] for global health status/quality of life (GHS/QoL). These were fatigue, nausea/vomiting, dyspnoea, and appetite loss. The company stated that the [redacted] (as measured by a 10-point difference) [redacted] did not provide point estimates or interval data for the EAG to critique. The

company did present the median time-to-definitive deterioration (TTDD) in GHS/QoL, which was [redacted] for the talazoparib arm than the placebo arm ([redacted] months vs [redacted] months; [redacted]).

Pain symptoms were measured using Brief Pain Inventory – Short Form (BPI-SF). There did [redacted] between the treatment arms but it was not clearly reported. Overall, poor reporting of the patient reported outcomes in the CS led to some uncertainty in the efficacy of talazoparib with enzalutamide versus placebo with enzalutamide. Better reporting would have also supported a more transparent comparison of patient reported outcomes in people treated with talazoparib with enzalutamide in the TALAPRO-2 trial and people treated with olaparib with abiraterone in the PROpel trial.

Figure 1: Plot of EQ-5D-5L index scores change from baseline in the Cohort 1 Part 2 PRO population (reproduced from Figure C, Doc B)

Abbreviations: . EQ-5D-5L, EuroQol five dimension (five level); PRO, patient reported outcomes

3.4.3. Safety

The company presented adverse reactions to treatment in Section B.3.10 of the CS.

3.4.3.1. Extent of exposure

The duration of exposure to study drugs in TALAPRO-2 is detailed below in Table 6. No time to treatment discontinuation (TTD) curves were presented in the CS.

At the data cutoff date of 16 August 2022 (median follow-up for the primary analysis: 24.9 months for the talazoparib arm, 24.6 months for the placebo arm), the mean duration of

treatment was 79.8 weeks for talazoparib and 71.7 weeks for placebo, with a mean relative dose intensity of [redacted]% and [redacted]%, respectively. The company presented the median, rather than mean, duration of treatment for enzalutamide. This was 96.6 weeks and 72.0 weeks in the talazoparib with enzalutamide and placebo with enzalutamide arms, respectively (median relative dose intensity: 99.9% versus 100.0%).

There were one third more AEs resulting in permanent drug discontinuation of talazoparib as compared to placebo (19.1% versus 12.2%), though discontinuations of enzalutamide due to AEs was the same for each arm. There were a substantially higher number of dose interruptions and dose reductions for talazoparib than placebo, primarily due to adverse events, and there were also twice as many dose interruptions (39% versus 19%) and dose reductions (15% versus 8%) of enzalutamide in the talazoparib arm compared to enzalutamide in the placebo arm.

Table 6: TALAPRO-2: Summary of the drug dosing exposure for the safety population (adapted from Tables 27 and 28, Doc B and Tables 18 and 19, CSR)

	Talazoparib with enzalutamide (n=398)	**Placebo with enzalutamide (n=401)**	**Total (n=799)**
Duration of treatment,[a] weeks			
N	397	400	797
Mean (SD)	79.8 (46.9)	71.7 (45.5)	75.7 (46.3)
Median (range)	86.0 (0.29, 186.1)	69.9 (2.1, 182.0)	74.6 (0.29, 186.1)
Relative dose intensity talazoparib/placebo[b] (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	83.5 (17.7, 104.5)	100.0 (53.5, 142.9)	[redacted]
Relative dose intensity enzalutamide (%)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	99.9 (31.1, 100.0)	100.0 (40.0, 100.1)	100 (31.1, 100.1)
Dose interruptions talazoparib/placebo, n (%)	268 (67.3)	134 (33.4)	402 (50.3)
Due to AE	235 (59.0)	68 (17.0)	303 (37.9)
Due to other reasons	110 (27.6)	80 (20.0)	190 (23.8)
Dose interruptions due to AE enzalutamide, n (%)	191 (48.0)	122 (30.4)	313 (39.2)
Due to AE	136 (34.2)	64 (16.0)	200 (25.0)
Due to other reasons	101 (25.4)	73 (18.2)	174 (21.8)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)	Total (n=799)
Dose reductions talazoparib/placebo, n (%)	218 (54.8)	45 (11.2)	263 (32.9)
Due to AE	209 (52.5)	28 (7.0)	237 (29.7)
Due to other reasons	13 (3.3)	11 (2.7)	24 (3.0)
Dose reductions due to AE enzalutamide, n (%)	74(18.6)	49(12.2)	123 (15.4)
Due to AE	58(14.6)	31 (7.7)	89(11.1)
Due to other reasons	14(3.5)	13 (3.2)	27 (3.4)
AE resulting in permanent drug discontinuation of:			
Talazoparib or placebo,[c] n (%)	75 (18.8)	49 (12.2)	124 (15.5
Enzalutamide,[d] n (%)	43 (10.8)	44 (11.0)	87 (10.9)

[a] Treatment duration (weeks) is defined as (date of last dose – date of first dose +1)/7.

[b] Relative dose intensity (%) is defined as the ratio of the actual dose intensity to the planned dose intensity expressed in %.

[c] Includes permanent discontinuation, dose reduction, or dose interruption of talazoparib or placebo with permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide.

[d] Includes permanent discontinuation, dose reduction, or dose interruption of enzalutamide only plus permanent discontinuation, dose reduction, or dose interruption of both talazoparib or placebo and enzalutamide.

Abbreviations: AE, Adverse event; SD, Standard deviation.

3.4.3.2. Adverse events

Talazoparib with enzalutamide demonstrated a substantially higher adverse event (AE) burden than placebo with enzalutamide. Thirty-nine percent of participants in the talazoparib with enzalutamide arm experienced a serious AE compared with 27% in the placebo with enzalutamide arm. The EAG's clinical experts stated that this level of toxicity was as expected for the combination treatment. The most common Grade ≥3 event was anaemia; this was experienced by 185 (46.5%) of participants on the talazoparib with enzalutamide and in 17 (4.2%) in the placebo with enzalutamide arm. While this was a high proportion of people in the intervention arm, the EAG's clinical expert noted that anaemia can develop over a number of months and can be corrected without a need to limit or interrupt their dose. However, they also stated that it is important to make people aware of the medication toxicity and the efficacy of the treatment for them, i.e. a reduced effect if their tumour is HRR non-deficient, to support patient choice.

Table 7: Summary of AEs for the safety population (N=799) (adapted from Table 28, Doc B)

	Talazoparib with enzalutamide (n=398)		Placebo with enzalutamide (n=401)	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE, n (%)	392 (98.5)	299 (75.1)	379 (94.5)	181 (45.1)
Treatment-related, AE, n (%)	357 (89.7)	234 (58.8)	279 (69.6)	71 (17.7)
Serious AE, n (%)	157 (39.4)	145 (36.4)	107 (26.7)	94 (23.4)
Serious and treatment-related AE, n (%)	78 (19.6)	68 (17.1)	12 (3.0)	11 (2.7)
Grade 5 AE, n (%)	13 (3.2)[a]	-	18 (4.5)[b]	-
Most common AE (all grades in ≥10% of participants),[c] n (%)				
Anaemia	262 (65.8)	185 (46.5)	70 (17.5)	17 (4.2)
Neutropenia	142 (35.7)	73 (18.3)	28 (7.0)	6 (1.5)
Fatigue	134 (33.7)	16 (4.0)	118 (29.4)	8 (2.0)
Thrombocytopenia	98 (24.6)	29 (7.3)	14 (3.5)	4 (1.0)
Back pain	88 (22.1)	10 (2.5)	72 (18.0)	4 (1.0)
Leukopenia	88 (22.1)	25 (6.3)	18 (4.5)	0

Data are n(%). Shown are AEs that occurred from the time of the first dose of study treatment through to 28 days after permanent discontinuation of all study treatments or before initiation of a new antineoplastic or any investigational therapy, whichever occurred first. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

[a] None were considered treatment-related.

[b] Two were considered treatment-related.

[c] None of these events were recorded as grade 5.

Abbreviations: AE, adverse event.

3.4.3.3. Skeletal related events

Skeletal related events (SREs) were reported in Section B.3.10.4 of the CS. SREs were reported [redacted] for participants in the talazoparib with enzalutamide treatment arm than for participants in the placebo with enzalutamide treatment arm.

Table 8: Summary of SREs for the safety population (N=799; reproduced from Table 30, Doc B)

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)
Any SRE (%)	[redacted]	[redacted]
Non-symptomatic fracture (%)	[redacted]	[redacted]
Radiotherapy to bone (%)	[redacted]	[redacted]
Spinal cord compression (%)	[redacted]	[redacted]
Surgery to bone (%)	[redacted]	[redacted]

	Talazoparib with enzalutamide (n=398)	Placebo with enzalutamide (n=401)
Symptomatic fracture (%)	[redacted]	[redacted]

Participants are only counted once per treatment event. MedDRA v25 coding dictionary applied.

Abbreviations: SRE, Skeletal related event.

3.5. NMA

The company presented an NMA comparing talazoparib with enzalutamide to olaparib with abiraterone for rPFS, OS, time to PSA, PSA response, and ORR. The additional interventions used to make the network were abiraterone monotherapy, enzalutamide monotherapy, and best supportive care (BSC). Eight RCTs were included in the NMA and the treatments evaluated in each trial are detailed in Table 9. The company presented network diagrams for each outcome in Section B.3.9.1 of the CS.

The company had previously undertaken what they referred to as the "original NMA"[9] which was a large NMA that included treatments that were not relevant to this submission. The company used a subset of that NMA for this submission and updated the searches to ensure no new evidence was missed. The EAG were not able to comprehensively assess whether all relevant studies included in the "original NMA" were also included in the NMA used for this submission. As noted in Section 3.1.1, the EAG found NCT02125357,[10]a relevant RCT in the wider network was not used in the NMA for this submission. However, the company later acknowledged this was a typographical error in the CS and that the NCT02125357 trial did not report rPFS.

Table 9: Summary of the trials used to carry out the NMA update (reproduced from Table 15, Doc B)

Trial	Intervention				
	TALA +ENZA	AAP	BSC	ENZA	OLAP +AAP
TALAPRO-2 (NCT03395197)[7]	✓			✓	
BRCAAway (NCT03012321)[11,12]		✓			✓
COU-AA-301 (NCT00638690) / COU-AA-302 (NCT00887198)[13]		✓	✓		
Hu 2020 (NR)[14]		✓	✓		
JNJ-212082 (NCT01591122)[15]		✓	✓		
PREVAIL (NCT01212991)[16]			✓	✓	
PROpel (NCT03732820)[8]		✓			✓
Pu 2022 (NCT02294461)[17]			✓	✓	

Abbreviations: AAP, Abiraterone acetate PO QD 1000 mg + Prednisone/Prednisolone 5 mg PO BID/10 mg PO QD; BSC, Best supportive care (Placebo, Prednisone 5 mg PO BID, Hydrocortisone 40 mg PO QD, and

Prednisolone 5 mg PO BID); ENZ, Enzalutamide 160 mg PO QD; NMA, Network meta-analysis; OLAP, Olaparib 300 mg PO BID; TALA, Talazoparib 0.5 mg QD.

3.5.1. Studies included in the NMA

An overview of the eight trials used in the NMA is provided in Table 10. This table was adapted from information presented in Table 8 in Appendix D of the CS and the company's response to clarification question A4. The key outcome in the NMA was rPFS and the EAG found the definition of rPFS to be similar across all five trials in the network.

Table 10: Clinical evidence included in the NMA

Study name and acronym	Study design	Population	Intervention	Comparator	Notes
BRCAAway (NCT03012321)[11,12]	Open label RCT	Adults with mCRPC. ECOG 0-2 61 analysed	Abiraterone with prednisone	Olaparib + abiraterone with prednisone	No prior PARP inhibitors, chemotherapy, enzalutamide.
COU-AA-301 (NCT00638690)[13]	Quadruple blinded RCT	Adults with mCRPC. ECOG 0-1 220 analysed	Abiraterone with prednisone	Placebo with prednisone	No prior cytotoxic chemotherapy, ketoconazole, or abiraterone.
Hu 2020[14]	Double-blind RCT.	Adults with mCRPC. 262 analysed	Abiraterone with prednisone	Placebo with prednisone	No prior chemotherapy.
JNJ-212082 (NCT01591122)[15]	Quadruple blinded RCT	Adults with mCRPC. ECOG 0-1 313 analysed	Abiraterone with Prednisone	Placebo with Prednisone	No prior cytotoxic chemotherapy, radiation therapy for mCRPC.
PREVAIL (NCT01212991)[16]	Double-blind RCT.	Adults with mCRPC. ECOG 0-1 1717 analysed	Enzalutamide + ADT	Placebo + ADT	No prior cytotoxic chemotherapy, ketoconazole, or abiraterone.
PROpel (NCT03732820)[8]	Double-blind RCT.	Adults at first line treatment of mCRPC. ECOG 0-1. 796 analysed	Olaparib + abiraterone with prednisone	Placebo + abiraterone with prednisone	Treatment naive in the mCRPC state
Pu 2022 (NCT02294461)[17]	Quadruple blinded RCT	Adults with mCRPC. ECOG 0-1 395 analysed	Enzalutamide	Placebo	No prior cytotoxic chemotherapy

Study name and acronym	Study design	Population	Intervention	Comparator	Notes
TALAPRO-2 (NCT03395197)[7]	Double-blind RCT.	Adults with mCRPC. ECOG 0-1	Talazoparib + enzalutamide	Placebo + enzalutamide	Treatment naive in the mCRPC state

Abbreviations: ADT, androgen deprivation therapy; CS,company submission; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; NMA, network Meta-Analysis; PARP, Poly-ADP ribose polymerase; RCT, randomised controlled trial.

3.5.2. Methodology of the pivotal trials

An overview of the methods used in the pivotal trial for talazoparib with enzalutamide (TALAPRO-2), and the pivotal trial for the comparator treatment, olaparib with abiraterone (PROpel), is provided in Table 11. The EAG's clinical experts noted that the eligibility criteria were similar for each trial. Both trials recruited men with mCRPC with progressive disease and an ECOG performance status of 0 or 1. Randomisation in TALAPRO-2 was stratified by homologous recombination repair (HRR) gene alteration status (deficient vs non-deficient or unknown), and both trials undertook subgroup analysis in people based on the tumour's HRR status.

Table 11: Comparative summary of trial methodology

Study	TALAPRO-2: NCT03395197[7]	PROpel: NCT03732820[8]
Location	287 sites in 26 countries in North America, Europe (including UK locations), Israel, South America, South Africa, and the Asia-Pacific region.	132 centres in 17 countries in North America, Australia, Europe (including UK locations), South America, Asia-Pacific region.
Trial design	Randomised, double-blind, placebo-controlled, Phase 3 study	Randomised, double-blind, placebo-controlled, Phase 3 study
Number of participants	N=805 (cohort 1[a])	N=796
Eligibility criteria	- Adults with histologically or cytologically confirmed adenocarcinoma of the prostate without small cell or signet cell features. - Metastatic disease in bone documented on bone scan or in soft tissue documented on CT/MRI scan; - Surgically or medically castrated, with serum testosterone ≤50 ng/dL at screening; - Progressive disease at study entry in the setting of medical or surgical castration; - ECOG performance status ≤1;	- Adults with histologically or cytologically confirmed prostate adenocarcinoma. - Metastatic status defined as at least 1 documented metastatic lesion on either a bone scan or a CT/MRI scan; - Documented evidence of progressive disease at study entry; - Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment. - ECOG performance status ≤1;

Study	TALAPRO-2: NCT03395197[7]	PROpel: NCT03732820[8]
	- Life expectancy ≥12 months as assessed by the investigator.	- Life expectancy ≥6 months as assessed by the investigator.
Exclusion criteria	- Any prior systemic cancer treatment initiated in the nonmetastatic CRPC or mCRPC disease state. (ADT and first-generation anti-androgens received in the CRPC disease state were **not** exclusionary); - Prior docetaxel for mCSPC was allowed if more than 4 weeks had elapsed from the last dose of docetaxel.	- People should not have received any cytotoxic chemotherapy, ARPis, or other systemic treatment in the mCRPC setting. ADT was an exception; - Treatment with first-generation antiandrogen agents before randomisation was allowed, but there must have been a washout period of 4 weeks.
Interventions evaluated	Talazoparib (0.5 mg/day) + enzalutamide (160mg/day) versus Placebo + enzalutamide enzalutamide (160mg/day)	Olaparib (300 mg twice daily) + abiraterone (1000mg once daily) and prednisolone (5mg twice daily)"versus Placebo + abiraterone (1000mg once daily) with prednisone (1000mg once daily)
Concomitant medication	Prohibited: prednisone >10 mg once daily, cytotoxic chemotherapy, hormonal therapy, other PARP inhibitor. Permitted: bisphosphonates or denosumab, ADT, hematopoietic growth factors, ESAs or RBC transfusions.	Prohibited: concurrent anticancer therapy, including investigational agents, while on study treatment. However, continuous ADT with an LHRH agonist/antagonist must be continued during the trial. Permitted: bisphosphonates or denosumab for bone disease.
Primary outcomes	BICR-assessed rPFS or death	Investigator-assessed ibPFS or death
Key secondary outcomes	- Overall survival (OS) - Investigator-assessed rPFS - Overall response rate (ORR) - PSA response - Time to confirmed PSA progression - Quality of life using EQ-5D-5L - Cancer-specific global health status/QoL, functional scales, and symptom scales (EORTC-QLQ-C30) - Adverse events	- Time to first subsequent anticancer therapy or death (TFST) - Overall survival (OS) - Time to second progression or death (PFS2) - Quality of life using EQ-5D-5L - Functional Assessment of Cancer Therapy Prostate Cancer (FACT-P) - Adverse events
Selected ore-planned subgroups	- HRR status (HRR deficient and HRR non-deficient / unknown) - Renal impairment (moderate, mild, normal) - Race (Asian, White, African American, other) - Prior NHT/ ARPi (yes, no)	- HRR status (HRR deficient and HRR non-deficient / unknown) - ECOG performance status at baseline (0 or 1) - Age at randomisation (<65, ≥65) - Region - Race Baseline PSA

Study	TALAPRO-2: NCT03395197[7]	PROpel: NCT03732820[8]
	- Prior docetaxel (yes, no)	

Abbreviations: ADT, androgen deprivation therapy; ARPis, androgen receptor pathway inhibitors; BICR, Blinded independent central review; CRPC, castrate-resistant prostate cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; EQ-5D-5L, EuroQol five dimension (five level); ESA, erythropoietin stimulating agents; FACT-P, Functional Assessment of Cancer Therapy Prostate Cancer; HRR, homologous recombination repair; ibPFS, imaging-base progression free survival; LHRH, luteinizing hormone-releasing hormone; mCRPC, metastatic castration-resistant prostate cancer; MRI, magnetic resonance imaging; NHT, Novel hormonal therapy ; ORR, overall response rate; OS, overall survival; PARP, Poly ADP ribose polymerases; PFS2, time to second progression or death; PSA, prostate specific antigen; QoL, quality of life; RBC, red blood cells; rPFS, radiographic progression-free survival; TFST, time to first subsequent anticancer therapy or death.

Note(s): [a] Cohort 1 were recruited to the trial and were not selected based on their HRR status.

3.5.3. Baseline characteristics of participants in the pivotal trials

The baseline characteristics of the participants in the intervention groups in the pivotal trials are presented below in Table 12. The EAG's clinical experts noted that while the participants were similar, a higher proportion of TALAPRO-2 participants had ECOG performance status 1 and had previously received ARPis, while a lower proportion were HRR deficient. Thus, the participants in PROpel were slightly fitter and would be more responsive to PARP inhibitor treatment due to the higher proportion who were HRR deficient.

Table 12: Baseline characteristics of participants in TALAPRO-2 and PROpel

Characteristic	TALAPRO-2[7] Talazoparib with enzalutamide (n=402)	PROpel[8] Abiraterone and Olaparib (n=399)
Median age, years (range)	71 (66-76)	69.0 (43–91)
Gleason score ≥8, n (%)	281 (70)	265 (66.4)
Median baseline serum PSA, µg/L (range/IQR)	18.2 (range: 6.9-59.4)	17.90 (IQR: 6.09–67.00)
Disease site, n (%)		
Bone (including with soft tissue component)	349 (87)	349 (87.5)
Lymph node	147 (37)	215 (53.9) - Distant and locoregional
Visceral (lung)	45 (11)	40 (10.0)
Visceral (liver)	12 (3)	15 (3.8)
Other soft tissue	37 (9)	47 (11.8) - Prostate and adjacent structures
ECOG performance status, n (%)		
0 (normal activity)	259 (64)	286 (71.7)
1 (restricted activity)	143 (36)	112 (28.1)
Previous docetaxel treatment, n (%)	86 (21)	97 (24.3)

Characteristic	TALAPRO-2[7] Talazoparib with enzalutamide (n=402)	PROpel[8] Abiraterone and Olaparib (n=399)
Prior treatment with NHA/ARPis	23 (6)	1 (0.3)
HRR gene alteration status by prospective tumour tissue testing, n (%)		
Deficient	85 (21)	111 (27.8)
Non-deficient	207 (51)	279 (69.9)
Unknown	110 (27)	9 (2.3)

Abbreviations: ARPi, androgen receptor pathway inhibitor; ECOG, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; NHA, novel hormonal agents; PSA, prostate-specific antigen.

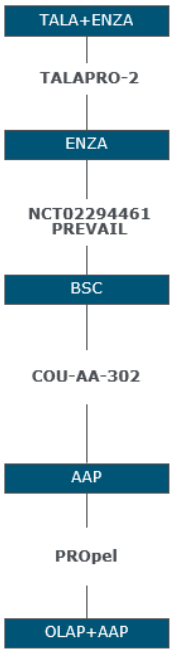
3.5.4. NMA methodology

Hazard ratios (HRs) and associated two-sided 95% confidence intervals (CIs) for comparisons in the network were estimated using a Bayesian framework and drawing on log hazard ratios extracted from the relevant trials. An underlying assumption of a Cox proportional hazards model is that the hazards for any two individuals have the same proportion at all times. Thus, the PH assumption implies the HR measuring the effect of any predictor is constant over time. The HRs from each study in the network can be checked for PH by plotting a log–log survival curve, using Schoenfeld residuals[18], or running a Grambsch and Therneau[19] test. When HRs are used in NMAs, the assumption of proportionality must hold across trials in the network for the resultant indirect comparison to generate a valid estimate of the HR.

3.5.5. rPFS and OS networks

The EAG will focus on the outcomes relevant to the cost minimization analysis: rPFS and OS. The network for these two outcomes is detailed below in Figure 2 and was an indirect comparison that did not contain any closed loops.

Figure 2: rPFS and OS network (N=5; reproduced from Figure 7, Doc B)



Abbreviations: OS, overall survival; rPFS, radiographic progression-free survival.

The EAG assessed the network based on the three assumptions underlying all indirect comparisons[20], and the PH assumption underlying a Cox proportional hazards model:

- All the trials included must be comparable in terms of potential effect modifiers (e.g. trial or patient characteristics) (assumption of **similarity**).
- There must be no relevant heterogeneity between trial results in pairwise comparisons (assumption of **homogeneity**).
- There must be no relevant discrepancy or inconsistency between direct and indirect evidence (assumption of **consistency**).
- The basic assumption in the **proportional hazards** model is that the hazard function in the 2 groups remains constant over time.

3.5.5.1. Similarity

The five trials used in the rPFS and OS NMAs recruited adults with mCRPC with an Eastern Cooperative Oncology Group (ECOG) Performance Status scale score of 0 or 1. The baseline characteristics were reported for three of the five trials in the network and the EAG presents potential effect modifiers in Table 13, below. The trials recruited men of similar age and the Gleeson score, a grading system for prostate cancer, was also similar between the three trials. However, disability as measured by the Eastern Cooperative Oncology Group

(ECOG) performance status, prior docetaxel treatment, and baseline prostate-specific antigen (PSA) all varied considerably between the trials. Also, there were potential effect modifiers that were not reported in each trial, such as Brief Pain Inventory (BPI), time since diagnosis, and the number of bone metastases. As noted in Chapter 2, PARP inhibitors (talazoparib and olaparib) are more efficacious when a person's tumour has a HRR deficient status. Twenty-one percent of participants in TALAPRO-2 were HRR deficient and 28% in PROpel were HRR deficient, offering a benefit to the comparator arm. Given the differences seen in the three trials that reported baseline characteristics, the EAG considered it likely there were further dissimilarities in effect modifiers in the two trials where baseline characteristics were not reported.

The EAG also assessed the rPFS definitions used in each of the five trials in the NMA. The EAG found the definitions to be broadly consistent with four trials quoting progression free survival (PFS) as per the RECIST 1.1 guidelines. The other trial, COU-AA-302, did not specify RECIST 1.1 guidelines, but noted that it was judged by blinded radiologist and referred to soft-tissue lesions measured using CT or MRI and bone scanning.

Overall, the EAG was concerned that the trials were quite different from each other in the distribution of the treatment effect modifiers that were reported, with increased concerns that there were further differences in treatment effect modifiers that were unclear due to inconsistent reporting by each trial.

Table 13: Notable baseline characteristics of participants in three trials in the rPFS and OS networks

	TALAPRO-2[7] Talazoparib with enzalutamide (n=402)	**PROpel**[8] Olaparib with abiraterone (n=399)	**Pu 2022**[17] Enzalutamide (n = 198)
Age, years, median (range)	71 (66–76)	69.0 (43–91)	71 (51–89)
A baseline ECOG performance status of 1, n (%)	143 (35.6%)	112 (28.1)	85 (42.9)
Time since diagnosis, months, median (range)	NR	NR	30.25 (0.4–161.9)
Prior docetaxel treatment	86 (21%)	97 (24.3)	0
Previous treatment with NHAs/ARPis, n (%)	23 (5.7)	1 (0.3)	0
H**R**R deficient	85 (21.1%)	111 (27.8)	NR
BPI-SF, question 3 (worst pain in last 24 h) score of 2-3, n (%)	NR	NR	62 (31.3)
Baseline PSA, µg/L, median (range/IQR)	18.2 (IQR: 6.9-59.4)	17.90 (IQR: 6.09–67.00)	56.2 (range: 2.5–5000.0)
Total Gleason score 8-10, n (%)	281 (69.9)	265 (66.4)	138 (69.7)
>20 bone metastases at screening, n (%)	NR	NR	32 (16.2)

Abbreviations: ARPis, androgen receptor pathway inhibitors; BPI-SF, Brief Pain Inventory-Short form; ECOG, Eastern Cooperative Oncology Group; NHA, novel hormonal agents; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

3.5.5.2. Homogeneity

Homogeneity could only be assessed in relation to PREVAIL and Pu 2022 as both evaluated enzalutamide versus placebo. The trials showed no relevant heterogeneity in rPFS results (HR: 0.32; 95% CI 0.28, 0.37 and HR: 0.31; 95% CI0.2, 0.46). However, they did have heterogeneity in relation to their OS results. Pu 2022 (HR: 0.33; 95% CI 0.16, 0.67) found a much stronger effect than PREVAIL (HR: 0.73; 95% CI 0.63, 0.85).

3.5.5.3. Consistency

There were no closed loops in the rPFS or OS networks and it was not possible to assess the consistency of the direct and indirect evidence.

3.5.5.4. Proportional hazards assumption

The Cox model relies on the assumption of proportional hazards (PH) across different covariates. For the purposes of this analysis, the covariates were the efficacy data (HRs) from each of the studies in the network. The PH assumption can be checked for each study using a visual assessment of Kaplan-Meier (KM) curves, log(−log) plots, and testing of scaled Schoenfeld residuals. The company did not present any assessment of the PH assumption for the input data to the NMA in the CS.

The EAG assessed the KM curves for rPFS and OS from the trials used in the rPFS and OS network. The OS curves did not meet the assumption of PH and it was unclear whether the rPFS curves met the assumption. The EAG checked the publications, and where possible the NICE technology appraisals, of the trials used in the rPFS and OS network for published evaluations of the PH. The PH assumption for rPFS and OS in the PROPel trial (olaparib with abiraterone versus placebo with abiraterone) was checked for TA951[21].

An assessment of PH for rPFS was presented in Section B.3.3.2.1 of the CS for TA951. The company found that the Schoenfeld residuals plot for PFS (plot redacted) showed a non-linear trend line and a non-zero gradient for residuals against time indicating that the proportional hazards assumption may not hold, and noted that this was supported by the log-cumulative hazards plot (plot redacted) showing non-parallel trendlines between arms. They concluded that individual fitted models should be preferred to joint models.

An assessment of PH for OS was presented in Section B.3.3.1.1 of the CS for TA951. The Schoenfeld residuals plot showed a non-linear and non-zero gradient for residuals against time, indicating that an assumption of proportional hazards between the two trial arms may not hold (plot redacted). This was again supported by the log-cumulative hazards plot, which showed non-parallel trendlines between arms (plot redacted) indicating that individual fitted models may be more appropriate for extrapolating each arm rather than jointly fitted models.,

Given the EAG's assessment of the KM plots for rPFS and OS from the individual studies in the NMA, and the assessment of PH in the PROpel trial in TA951, the EAG do not consider a Cox proportional hazards model to be a robust method of assessment for this NMA. Violating the PH assumption can lead to biased estimates and inaccurate conclusions and the company should replace their Cox proportional hazards model by using either an unanchored matching-adjusted indirect comparison (MAIC) based method or fractional polynomials.

3.5.6. Model fit and heterogeneity

In Section B.3.9.4 of the CS, the company reported on the model fit and heterogeneity of the Bayesian models tested for each outcome. For each outcome at least two models were tested, based on different priors and/or a different number of trial inputs.

For each model, the absolute goodness-of-fit was checked by comparing the total residual deviance to the total number of data points included in an analysis. Possible inconsistency between the direct and indirect evidence was not assessed due to the absence of closed loops in the networks. On the basis of checks on the model fit and heterogeneity presented in Table 26 in Document B, the company decided to use the log_normal(-2.56, 1.74) between-trial variance prior model for all outcomes. This was an off-the-shelf prior and the EAG did not consider it to be inappropriate.

However, given the network for rPFS and OS was a straight line consisting of single studies at all but one comparison, the EAG noted that the random effect estimated relies on one comparison in the network with only two studies. Therefore, given the shape and number of studies in the network, the EAG considered the fixed effect (FE) model may provide a better fit. At the clarification stage (A6), the EAG requested analysis using uninformative priors in a RE model and analysis using a FE model be presented to ensure the best fitting model was used (Table 14).

For rPFS, the data were best fit by the FE model according to the total residual deviance (totresdev) and the deviance information criterion (DIC). Given the FE model fit the data best and the number of studies in the network, the EAG consider the FE model to be the most appropriate for rPFS. For OS, the uninformative prior best fit the data based on the totresdev and DIC, however it had substantially higher between study SD than the company's preferred RE model (log_normal(-2.56, 1.74)). The FE model has a higher total residual deviance and DIC but the EAG considered the results to be of note given the shape and number of studies in the network.

Table 14: Model fit and heterogeneity for all analyses (reproduced from Table 12 in the clarification response)

Analysis			Absolute model fit		DIC	Between study SD (95% CrI)
Outcome variable	N	Prior	Totresdev	Data points		
rPFS	5	NR (FE)	3.9	5	7.8	NR
	5	half_normal(0, 5)	4.7	5	9.4	0.59 (0.02, 6.36)
	5	log_normal(-3.95,1.79)	4.10	5	8.30	0.01 (0.00,0.23)
	5	log_normal(-2.56, 1.74)	4.20	5	8.50	0.04 (0.00,0.42)
OS	5	NR (FE)	8.4	5	12.4	NR
	5	half_normal(0, 5)	5.2	5	10.4	1.42 (0.12, 8.30)
	5	log_normal(-3.95,1.79)	Not appropriate. Model convergence issues			
	5	log_normal(-2.56, 1.74)	6.80	5	11.7	0.14 (0.00,1.57)

Abbreviations: CrI, credible interval; DIC, deviance information criterion; FE, fixed-effect; NR, not required; OS, overall survival; rPFS, radiographic progression-free survival; SD, standard deviation; Totresdev, total residual deviance.

3.5.7. NMA results

Results were presented using the posterior median treatment effects, 95% credible intervals (CrI) and 95% prediction intervals (PrI). The 95% PrI indicates the extent of between-study heterogeneity by illustrating the range of HRs that might be expected in a future study. The company presented results for analysis using the RE model with a log_normal(-2.56, 1.74) between-trial variance prior in the CS. At the clarification stage, they also presented results using a RE model using another informative prior log_normal(-3.95,1.79) prior, a RE model using uninformative prior half_normal(0, 5), and results using a FE model with no between-trial variance prior. As noted in Section 3.5.6, given the shape and number of studies in the network and the absolute model fit, the EAG considered the FE model to be the most appropriate for rPFS. However, the company considered the RE model using the log_normal(-2.56, 1.74) prior to be the most appropriate and the EAG has presented the results of both models in the following sections.

3.5.7.1. Radiological Progression Free Survival

There were five studies in the network for rPFS. The NMA using the FE model found talazoparib with enzalutamide [redacted] olaparib with abiraterone for rPFS (olaparib with abiraterone versus talazoparib with enzalutamide [redacted]). The EAG also noted that [redacted] had a numerical benefit over [redacted].

Figure 3: Forest plot of comparators vs talazoparib with enzalutimide for rPFS (FE model; reproduced from Figure 3 in the clarification response)

Abbreviations: BSC, best supportive care; AAP, abiraterone (and prednisone); ENZA, enzalutimide; olaparib with abiraterone (and prednisone); FE, fixed effect; HR, hazard ratio; OS, overall survival; rPFS, radiological progression-free survival; TALA+ENZA, talazoparib with enzalutamide.

The NMA using a RE model and log_normal(-2.56, 1.74) prior found talazoparib with enzalutamide had a [redacted] olaparib with abiraterone ([redacted]). The EAG noted that the efficacy of [redacted] was similar to [redacted]. The NMA found there was a [redacted]% probability that talazoparib with enzalutamide was the best treatment for rPFS, a [redacted]% probability that olaparib with abiraterone was the best treatment and a [redacted]% probability that enzalutamide monotherapy was the best treatment.

3.5.7.2. Overall Survival

The same five studies in the rPFS network informed the OS network. The NMA using the FE model found a

[redacted]

([redacted]). The EAG agree with the company that this demonstrated [redacted] intervention and comparator for the OS. However, as the company noted in Section B.3.6.3 of the CS, the OS data in TALAPRO-2 were immature with only [redacted] of patients in the talazoparib with enzalutamide arm and [redacted] of patients in the placebo with enzalutamide arm having died at the data cutoff. This led to wide confidence intervals around the point estimate and the EAG was uncertain of whether there was [redacted] in OS between the two treatments.

Figure 4: Forest plot of HR vs TALA+ENZA for OS (FE model; reproduced from Figure 6 in the clarification response)

Abbreviations: BSC, best supportive care; AAP, abiraterone (and prednisone); ENZA, enzalutimide; olaparib with abiraterone (and prednisone); FE, fixed effect; HR, hazard ratio; OS, overall survival; rPFS, radiological progression-free survival; TALA+ENZA, talazoparib with enzalutamide.

The NMA using a RE model with log_normal(-2.56, 1.74) prior also found there was [redacted] talazoparib with enzalutamide and olaparib with abiraterone for OS ([redacted]). There was a [redacted]% probability talazoparib with enzalutamide was the best treatment for OS, a [redacted]% probability that olaparib with abiraterone was the best treatment, a [redacted]% probability that enzalutamide monotherapy was the best treatment, a [redacted]% probability that abiraterone was the best treatment, and a [redacted]% probability best supportive care was the best treatment.

3.5.7.3. Additional NMA results

The company also presented NMA results for:

- Time to prostate-specific antigen (PSA) progression
- PSA response
- Objective response rate (ORR)

These were presented for the RE model using informative priors, log_normal(-2.56, 1.74) and normal(-3.95,1.79), in Section B.3.9.3 of the CS. Results for the RE model using an uninformative prior, half_normal(0, 5), and results for the FE model, were presented in the company's clarification response (A6).

3.6. Safety of talazoparib with enzalutamide and olaparib with abiraterone

In this section, the EAG compared the safety reported in the talazoparib with enzalutamide arm in the TALAPRO-2 trial with the olaparib with abiraterone arm in the PROpel trial.

3.6.1. Drug dosing exposure

The drug exposure of the intervention arms reported in the TALAPRO-2 trial[7] and in the PROpel trial[8] are presented below in Table 15. No TTD was reported but the median time on treatment with talazoparib (86 weeks) or olaparib (~79 weeks) were similar between the treatment arms. There were higher rates of dose interruptions, dose reductions, and drug discontinuations, due to adverse events, for talazoparib than olaparib. In addition, a higher proportion of people on enzalutamide than abiraterone had dose interruptions, dose reductions, and drug discontinuations. However, the EAG caution that there were differences in the populations recruited to each trial and this was a naïve comparison between the trials.

Table 15: Summary of the drug dosing exposure for the intervention arms in the TALAPRO-2 and PROpel trials

	Talazoparib with enzalutamide (n=398)[22]	Olaparib with abiraterone (n=398)[8]
Duration of treatment with talazoparib/olaparib		
N	397	397
Mean (SD)	79.8 (46.9) weeks	NR
Median (range)	86.0 (0.29, 186.1) weeks	17.5 months or ~76 weeks
Dose interruptions talazoparib/olaparib, n (%)	268 (67.3)	NR
Due to AE	235 (59.0)	178 (44.7)
Due to other reasons	110 (27.6)	NR
Dose interruptions due to AE enzalutamide/abiraterone, n (%)	156 (39.1)	131 (32.9)
Dose reductions talazoparib/ olaparib, n (%)	218 (54.8)	NR
Due to AE	209 (52.5)	80 (20.1)
Due to other reasons	13 (3.3)	NR
Dose reductions due to AE enzalutamide/abiraterone, n (%)	58 (14.6)	10 (2.5)
AE resulting in permanent drug discontinuation of:		
Talazoparib/olaparib, n (%)	75 (18.8)	55 (13.8)
Enzalutamide/abiraterone, n (%)	43 (10.8)	34 (8.5)

Abbreviations: AE, Adverse event; NR, not reported; SD, Standard deviation.

3.6.2. Adverse events

A summary of adverse events (AEs) in the talazoparib with enzalutamide arm of the TALAPRO-2 trial and the olaparib with abiraterone arm of the PROpel trial is presented below in Table 16. There was a substantially higher rate of Grade ≥3 adverse events in the talazoparib with enzalutamide arm (299, 75.1%) compared to the olaparib with abiraterone arm (188, 47.2%). There was also a higher rate of serious AEs (39% versus 33.9%). There were a higher proportion of Grade ≥3 anemia, fatigue, back pain, and hypertension events in the talazoparib with enzalutamide arm than the olaparib with abiraterone arm. As previously noted, there were differences in the populations recruited to each trial and this was a naïve comparison between the trials. However, despite the differences in populations recruited, the EAG considered this to be evidence that talazoparib with enzalutamide had a higher drug toxicity than olaparib with abiraterone.

Table 16: Summary of adverse events occurring in the intervention arms in the TALAPRO-2 and PROpel trials

	Talazoparib with enzalutamide (n=398)[22]		**Olaparib with abiraterone (n=398)[8]**	
	All grades	**Grade ≥3**	**All grades**	**Grade ≥3**
Any AE, n (%)	392 (98.4)	299 (75.1)	387 (97.2)	188 (47.2)
Treatment-related AE, n (%)	357 (90.0)	234 (58.8)	NR	NR
Serious AE, n (%)	157 (39.4)	145 (36.4)	135 (33.9)	NR
Serious and treatment-related AE, n (%)	78 (20.0)	68 (17.1)	NR	NR
Grade 5 AE, n (%)	13 (3.3)	-	NR	NR
Common AEs (all AEs in ≥10% of total participants), n (%)				
Anaemia	262 (65.8)	185 (46.5)	183 (46.0)	60 (15.1)
Neutropenia	142 (35.7)	73 (18.3)	NR	NR
Fatigue	134 (33.7)	16 (4.0)	148 (37.2)	9 (2.3)
Thrombocytopenia	98 (24.6)	29 (7.3)	NR	NR
Back pain	88 (22.1)	10 (2.5)	68 (17.1)	3 (0.8)
Leukopenia	88 (22.1)	25 (6.3)	NR	NR
Decreased appetite	86 (21.7)	5 (1.3)	58 (14.6)	4 (1.0)
Hypertension	55 (13.8)	21 (5.3)	50 (12.6)	14 (3.5)
Venous embolic and thrombotic events	NR	NR	29 (7.3)	27 (6.8)

Abbreviations: AE, adverse events; NR, not reported.

3.7. EAG conclusions on the clinical effectiveness of talazoparib with enzalutamide

Based on the above evidence, it was unclear to the EAG whether talazoparib with enzalutamide had similar efficacy and safety to olaparib with abiraterone in people with untreated mCRPC for whom chemotherapy is not clinically indicated.

The submission presented the efficacy and safety of talazoparib with enzalutamide versus placebo with enzalutamide in the TALAPRO-2 trial. TALAPRO-2 was a large well conducted trial in people with mCRPC. However, as explained in Section 2.1, the population recruited to the trial appeared, in the most part, to be eligible for chemotherapy (docetaxel) treatment. However, the EAG recognised that olaparib with abiraterone (TA951)[21] is recommended in a slightly broader population of adults who cannot have or do not want chemotherapy. The participants in TALAPRO-2 may be categorised as adults who do not want chemotherapy and chose ARPi or ARPi with PARP inhibitor therapy.

The TALAPRO-2 trial found talazoparib with enzalutamide to have a statistically significant benefit over placebo with enzalutamide for rPFS (HR: 0.63; 95% CI 0.51, 0.78) and to be equally effective for OS. Quality of life measured by EQ-5D-5L appeared to be [redacted]. PARP inhibitors (talazoparib and Olaparib) are known to be more effective in people with HRR deficient tumours. Subgroup analysis in TALAPRO-2 found the benefit of talazoparib with enzalutamide for rPFS to be reduced in people with HRR non-deficient/unknown tumours (HR: 0.70; 95% CI 0.54, 0.89) compared to people with HRR deficient tumours (HR: 0.48; 95% CI 0.31, 0.74).

The company undertook an NMA to compare talazoparib with enzalutamide (TALAPRO-2 trial) to olaparib with abiraterone (PROpel trial) for rPFS, OS, time to PSA, PSA response, and ORR. The network for rPFS and OS was a sparse network that used four comparisons across five studies to connect intervention and comparator. It was a straight line between intervention and comparator and did not have any closed loops The company conducted the NMA by using a Cox proportional hazards model within a Bayesian framework.

The Cox model relies on the assumption of proportional hazards (PH) across different covariates. The EAG found the input data into the rPFS and OS NMAs did not meet the PH assumption and this was notably checked for the PROpel trial (olaparib with abiraterone versus placebo with abiraterone) by the company in TA951[21]. Violating the PH assumption can lead to biased estimates and inaccurate conclusions. The EAG considered that NMAs based on proportional hazards were inappropriate and should be replaced by using either an

unanchored matching-adjusted indirect comparison (MAIC) based method or fractional polynomials.

The company preferred a RE model with an informative between-trial variance prior, but the EAG preferred the FE model that showed a better model fit for rPFS. The FE model found talazoparib with enzalutamide to have [redacted] olaparib with abiraterone for rPFS [redacted]. All the models presented in the CS, and at the clarification stage, found [redacted] to be [redacted] for OS.

Talazoparib with enzalutamide appeared to have increased toxicity compared to olaparib with abiraterone on the basis of a naïve comparison between the intervention arms in the TALAPRO-2 and PROpel trials. Permanent drug discontinuation was higher for talazoparib (18.8%) than olaparib (13.8%), and Grade ≥3 adverse events were experienced by 75.1% of participants in the talazoparib with enzalutamide arm and 47.2% of people in the olaparib with abiraterone arm. The EAG caution that there were differences in the populations recruited to each trial but considered this moderate evidence that talazoparib with enzalutamide has higher toxicity than olaparib with abiraterone.

In sum, the EAG did not consider the NMA undertaken by the company to be robust and should be replaced with a more appropriate method of comparison. However, on the basis of the flawed NMA presented, the FE estimate of effect [redacted] and found talazoparib with enzalutamide [redacted] olaparib with abiraterone for rPFS. Therefore, it was not appropriate to assume equal efficacy in the cost minimization analysis. The EAG had concerns over the similarity of safety between the intervention and comparator. In the naïve comparison of safety between the trials there was moderate evidence that talazoparib with enzalutamide had higher toxicity than olaparib with abiraterone leading to higher permanent drug discontinuations and increased Grade ≥3 AEs. Again, it was not appropriate to assume equal safety in the cost minimization analysis.

4. SUMMARY OF THE EAG'S CRITIQUE OF THE COST-EFFECTIVENESS EVIDENCE SUBMITTED

4.1. Company's cost comparison analysis

4.1.1. Overview of cost comparison

The company have submitted a cost-comparison analysis, which assumed that both treatments have the same time on treatment with this assumed to be the same as the time spent in rPFS. The EAG does not consider the assumption that the two treatments have the same rPFS to be realistic (section 3.7). The company assumed administration costs are null (all treatments are tablets). Adverse events and skeletal events were assumed similar in both arms and therefore were only included in scenarios. Drug costs and monitoring costs were included in the analysis. The model does not include the cost of subsequent therapies as the company assumes that the time spent in post progression and the type of subsequent therapies will be the same for both arms.

4.1.2. Technology costs

4.1.2.1. Monthly (cycle) drug costs and Dosing

The cost comparison model featured a lifetime horizon with a cycle length of 30 days. Talazoparib with enzalutamide and olaparib with abiraterone cycle costs were calculated through the estimation of the monthly number of tablets (dosages sourced from the SmPC), multiplied by the costs per tablet (costs per tablet were based on unit pack prices sourced from: British National Formulary 2024[23], eMIT National Database (2023)[24], and the National Schedule of NHS costs (2021-2022)[25]). A PAS with an [redacted] discount is currently in place for talazoparib which resulted in costs per cycle of [redacted] and £5,065.09 (the latter was calculated with list prices) for talazoparib with enzalutamide and olaparib with abiraterone respectively. All other treatments have discount PAS in place which have not been included in the calculations in this report and are instead presented for the Committee in the cPAS appendix. The costs presented in this report should therefore not be viewed as informative in relation to whether treatment with talazoparib with enzalutamide is cheaper than olaparib with abiraterone.

The company model assumed in the base case that people get the SmPC dose[3] in both treatment arms until progression or death. This does not include the impact of continuation beyond radiographic progression, dose interruptions or early discontinuation due to toxicity or other reasons. The latter two of these factors are often captured within the calculation of the relative dose intensity (RDI) for the trial. Following clarification questions, the company

included RDI inputs of [redacted] and 98.2% for talazoparib with enzalutamide and olaparib with abiraterone respectively (e.g. revised base case). This approach has been accepted by the EAG despite the use of median RDIs rather than the mean values as the mean RDI was not available for olaparib with abiraterone [redacted]. The EAG would note, however, that using the same RDI for all treatments within a combination is not ideal. [redacted].

Table 17: Acquisition costs of talazoparib with enzalutamide and olaparib with abiraterone used in the cost comparison analysis

	Talazoparib with enzalutamide		Olaparib with abiraterone		
	Talazoparib	**Enzalutamide**	**Olaparib**	**Abiraterone**	**Prednisolone**
Pharmaceutical formulation	0.25 mg tablets in 30 tablets pack	40 mg tablets in 112 tablets pack	150 mg tablets in 56 tablets pack	500 mg tablets in 56 tablets pack	5 mg tablets in 28 tablets pack
(Anticipated) care setting	Secondary care				
Acquisition cost per pack (excluding VAT)	List price £1,655 [redacted] with PAS	List price £2,734.67	List price £2,317.50	List price £91.60	List price £0.41
Method of administration	Oral				
Dose	0.5 mg	160 mg	300 mg	1,000 mg	5 mg
Dosing frequency	Once daily	Once daily	Twice daily	Once daily	Twice daily
Cost per cycle	[redacted] with PAS	£2,930	£4,966.07	£98.14	£0.88

Abbreviations: mg, milligram; PAS, patient access scheme; VAT, value added tax
Source: company submission (Table 31)

4.1.2.2. Time on treatment

Supported by the comparable efficacy assumption, the company used rPFS data from TALAPRO-2 trial as a proxy for modelling treatment duration for both talazoparib with enzalutamide and olaparib with abiraterone. The EAG is not satisfied with this approach to calculate treatment costs because:

1. rPFS may not be an appropriate proxy to time to discontinuation (TTD) as people can remain on treatment despite having radiographic progression or discontinue early due to toxicity. Furthermore, as Table 18 shows, people can stop one of the co-treatments but remain on the other for some time before changing to 2nd line (e.g. stop olaparib but continue with abiraterone / stop talazoparib but continue with enzalutamide). It is not clear if the difference between median dose exposure and median rPFS indicates a comparable pattern of discontinuation relative to rPFS in the two trials. See Table.
2. Section 3.5.7.1 details the EAG preference for the fixed effect [redacted] to model olaparib with abiraterone survival. This suggests that the olaparib with abiraterone rPFS survival curve is statistically significantly shorter from that of talazoparib with enzalutamide.

Table 18 Dose exposure of PROPEL and TALAPRO-2 trials (median duration in months)

Treatment arm	PROPEL[8] / TALAPAPRO-2[7] (median, months)		
	Component	**Dose exposure**	**rPFS**
Olaparib arm	Olaparib	17.5	24.8
	Abiraterone	18.2	
Placebo arm	Abiraterone	15.7	16.6
	Placebo	15.7	
Talazoparib arm	Talazoparib	19.8	Not reached (95% CI 27.5 – Not reached)
	Enzalutamide	22.2	
Placebo arm	Enzalutamide	16.6	21.9 (95% CI 16.6 - 25.1)
	Placebo	16.1	

Abbreviations: CI confidence interval; rPFS, radiographic progression-free survival
Sources: Clark (2022)[8] Efficacy section; Agarwal (2023)[7] Safety section

Treatments after progression were not accounted for in the model as it was assumed that people will receive the same second-line therapy irrespective of the intervention and comparator in the UK clinical setting. Based on clinical expert opinion, the EAG agrees that the subsequent therapy

would be the same for both treatments. However, the duration of subsequent therapy might not be the same, given the different rPFS.

4.1.2.3. rPFS extrapolation, treatment duration and OS assumptions

To model treatment duration beyond the observed data from TALAPRPO-2, the company fitted different parametric distributions to the latest PFS data. Model selection was based on the AIC and BIC criteria, visual inspection of KM plots overlaid with survival parametric curves, and long-term clinical plausibility. The model that presented the best fit was the gamma distribution, however, long-term survival estimates did not align with the feedback from UK clinical experts. Hence the log-normal distribution was used to estimate rPFS long term survival rates. The EAG agrees with this approach.

In relation to the treatment duration of olaparib with abiraterone, the EAG in its base case applied a HR of [redacted] (see section 4.1.2.2 above). It is strictly improper, from a statistical perspective, to apply an HR to an accelerated failure time distribution. However, given the limitations of the base case, the EAG considers this to be the best approach to differentiate both treatments.

Finally, the CS did not include any analysis of long-term OS data. The EAG would agree with the approach if the comparable efficacy assumption was met. As it was not, the EAG acknowledges this limitation of the base case and therefore assumed in its analyses that the discounted costs and benefits in both groups are the same with regards to the progressed disease state (e.g. health state after disease progression with the treatments in the appraisal).

4.1.3. Administration, monitoring costs and resource use

Administration costs were not considered in the economic case as all treatments are administered via tablets. The EAG considers that this is only reasonable if the treatments are equally effective. If not, pharmacy dispensing costs should be included. Monitoring costs were included as shown in Table 20.

Clinical expert opinion received by the EAG was that in the long term monitoring requirements would be the same for both treatments. In the short term (initial 12 weeks) there may be increased monitoring requirements associated with abiraterone but the impact of these on costs would not be expected to be large. Given this in the EAG base case we assumed equal resource use for both treatments rather than using the company assumption of different costs (Table 19).

Table 19: Monitoring costs

	Cost per cycle (First 3 months)	Cost per cycle (4+ months)	Discounted lifetime monitoring cost
Talazoparib with enzalutamide	£400.43	£231.23	£30,508.50
Olaparib with abiraterone	£419.44	£240.73	£31,119.61

Table 20: Monitoring requirements of talazoparib with enzalutamide and olaparib with abiraterone

	Talazoparib with enzalutamide				Olaparib with abiraterone			
	First 3 months		4+ months		First 3 months		4+ months	
Resource required	**% of patients per month**	**Frequency per month**	**% of patients per month**	**Frequency per month**	**% of patients per month**	**Frequency per month**	**% of patients per month**	**Frequency per month**
Outpatient visit (consultant led)	50%	2.175	50%	1.088	50%	2.175	50%	1.088
Outpatient visit (nurse led)	50%	2.175	50%	2.175	50%	2.175	50%	2.175
CT scan	100%	0.217	100%	0.217	100%	0.217	100%	0.217
Bone scan	20%	0.348	20%	0.348	20%	0.348	20%	0.348
Full blood count	100%	1	100%	1	100%	2.175	100%	1.088
Liver function test	0%	0	0%	0	100%	2.175	100%	1.088
Kidney function test	0%	0	0%	0	100%	2.175	100%	1.088
Treatment toxicity monitoring (first 12 months)	0%	0	0%	0	100%	1.001	100%	1.001
PSA test	100%	2.175	100%	1.088	100%	2.175	100%	1.088

Abbreviations: CT, Computed tomography; PSA, Prostate-specific antigen

4.1.4. Adverse event costs and skeletal related events

AEs were not included in the CS base case as the company assumed comparable safety. In scenario analysis, adverse event unit costs were retrieved from the National Schedule of NHS Costs Year: 2021-22 and adjusted to 2024 with the CPI index 06. Each adverse event was correctly linked to National Schedule codes; however, standard averages of costs were used rather than weighted averages (e.g. that consider the activity of that code). After a clarification question from the EAG, the company corrected this approach. The EAG is content with the revised methodology as AEs are only inputted to the first cycle and therefore do not have any impact in the long term.

SREs were also not included in the company's base case, although they were included in sensitivity analysis. In that scenario, the SREs related to olaparib were informed by four older RCTs in the mCRPC population that did not include olaparib with abiraterone as a treatment. The EAG does not consider this to be appropriate and similarly neither did clinical experts consulted by the EAG.

Overall, the EAG agrees with the non-inclusion of AEs and SREs in this cost comparison appraisal [redacted] and the evidence presented was not of sufficient quality to support a differential impact for SREs between treatments. The EAG does, however, note that there are indications of increased toxicity with talazoparib with enzalutamide which should be accounted for if a full cost-utility analysis is required in future.

4.1.5. Company results

Based upon the company's revised analysis, the total cost of talazoparib with enzalutamide is calculated as [redacted], of which 87.3% is the drug cost and 12.7% is the monitoring cost. Olaparib with abiraterone total costs were calculated as £344,235, of which 89.9% is the drug cost and 11.1% is the monitoring cost. These results were calculated using olaparib, abiraterone and enzalutamide list prices.

4.1.6. EAG base case

The EAG identified only minor calculation errors and unjustified changes in the revised model which did not impact the company base case (see Appendix A). These were corrected in the EAG revised model.

Within the EAG's analysis (which assumed a fixed effects hazard ratio of [redacted] for rPFS and TALAPRO-2 monitoring costs in both arms), the cost of olaparib with abiraterone significantly reduced to [redacted] at list price (Table **21**).

Table 21: EAG base case

Preferred assumption	Incremental costs vs olaparib with abiraterone
Company base case	[redacted]
Fixed effects rPFS HR	[redacted]
Monitoring resource use assumed equal in both arms	[redacted]
Cumulative impact of EAG preferred assumptions	[redacted]

Abbreviations: EAG, external assessment group; HR, hazard ratio; rPFS, radiographic progression free survival.

5. EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

5.1. Strengths

5.1.1. Clinical evidence

The company presented the efficacy and safety of talazoparib with enzalutamide versus placebo with enzalutamide in the TALAPRO-2[7] trial. TALAPRO-2 was a large well conducted trial in people with mCRPC. This trial found talazoparib with enzalutamide to be superior to placebo with enzalutamide for the primary outcome, radiologicical progression-free survival (rPFS; Section 3.4.1). It also found a similarity of effect between treartments for overall survival (OS) and similar quality of life via EQ-5D-5L (Section 3.4.2).

The company presented a network meta-analysis (NMA) comparing talazoparib with enzalutamide to olaparib with abiraterone, using a Cox proportional hazards model within a Bayesian framework. The company preferred a random effects model using an informative prior. This analysis found talazoparib with enzalutamide to have a [redacted] olaparib with abiraterone for rPFS, and found both treartments [redacted] in OS.

5.1.2. Economic evidence

The EAG did not identify any calculation errors in the model which impacted the company base case.

5.2. Weaknesses and areas of uncertainty

5.2.1. Clinical evidence

The EAG had minor concerns that, as discussed in Section 2.1, the population recruited to the TALAPRO-2[7] trial were not strictly ineligable for chemotherapy. However, the EAG was aware that people with mCRPC who were eligible for chemotherapy commonly chose to receive androgen receptor pathway inhibitors (ARPis; enzilutamide or abiraterone) instead. The participants in TALAPRO-2 may be categorised as adults who do not want chemotherapy and instead opted for ARPi or ARPi with PARP inhibitor therapy.

The three principle weaknesses and areas of uncertainty of the clinical evidence were linked to the NMA submitted by the company and are detailed below.

The shape and number of studies in the network

The rPFS/OS network was a straight line (Figure 2) containing only five studies across four comparisons (Section 3.5.5). Networks with this shape, where there are mostly one study for each comparison, are prone to bias through differences in treatment effect modifiers between the studies. In addition, because the network contained no closed loops, consistency between direct and indirect evidence could not be checked. In sum, the shape and number of studies in the network led to an analysis more prone to bias that can occur due to lack of similarity between studies, and with less facility to assess this bias in the analysis.

Cox proportional hazards model

The company conducted the NMA within a Bayesian framework assuming proportional hazards in HRs derived from Cox regressions. The Cox model relies on the assumption of proportional hazards (PH) across different covariates. The EAG found the input data into the rPFS and OS NMAs did not meet the PH assumption and this was notably checked for the PROpel trial[8] (olaparib with abiraterone versus placebo with abiraterone) by the company in TA951[21] (Section 3.5.5.4). Violating the PH assumption can lead to biased estimates and inaccurate conclusions.

Choice of meta-analysis and priors

The company preferred a random effects (RE) model with an informative between-trial variance prior, but the EAG preferred the FE model that showed a better model fit for rPFS (Section 3.5.6). The FE model found talazoparib with enzalutamide to have [redacted] olaparib with abiraterone for rPFS [redacted] found in the company's preferred model: [redacted]

A further weakness and area of uncertainty was the safety analysis presented in the CS. It was unclear to the EAG whether the intervention and comparator were similarly safe. On the basis of a naïve comparison between the intervention arms in the TALAPRO 2[7] and PROpel[8] trials, talazoparib with enzalutamide had increased toxicity compared to olaparib with abiraterone (Section 3.4.3).

5.2.2. Economic evidence

The weaknesses with the economic evidence mainly stem from the assumption that talazoparib with enzalutamide is similar to olaparib with abiraterone. This, along with the assumption that

rPFS and TTD are the same led to the assumption that the time on treatment for both types of treatment (and the individual components of those types of treatments) are the same. The EAG does not agree with this assumption and notes that time on treatment would be expected to be shorter for olaparib with abiraterone which reduces its treatment costs. Additionally, the EAG consider that there may be some difference in the time spent on subsequent treatment between arms in practice, however, the impact of this is expected to be limited as the same types of subsequent therapy are available after both combinations and comprise cheap generic treatments.

References

1. MHRA. Talazoparib: Summary of Product Characteristics. 2024.

2. National Institute for Health and Care Excellence. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer: Final scope. 2024.

3. Electronic Medicines Compendium. Docetaxel 20 mg/ml concentrate for solution for infusion (SmPC) 2023. Available from: https://www.medicines.org.uk/emc/product/7206/.

4. National Institute for Health and Care Excellence. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer (TA951). 2024.

5. Asim M, Tarish F, Zecchini HI. Synthetic lethality between androgen receptor signalling and the PARP pathway in prostate cancer. Nat Commun. 2017;8:374.

6. National Institute for Health and Care Excellence. 2.5 Critical appraisal of the relevant clinical effectiveness evidence. Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template: NICE process and methods [PMG24] 2022.

7. Agarwal N, Azad AA, Carles J. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. Lancet. 2023;402:291-303.

8. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, Oya M, Shore N, Loredo E, et al. Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer. NEJM Evidence. 2022;1(9):EVIDoa2200043.

9. Pfizer. NMA Final Technical Report. 2023.

10. Khalaf DJ, Annala M, Taavitsainen S, Finch DL, Oja C, Vergidis J, et al. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. The Lancet Oncology. 2019;20(12):1730-9.

11. Hussain MHA, Kocherginsky M, Agarwal N, Adra N, Zhang J, Paller CJ. BRCAAway: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) bearing homologous recombination-repair mutations (HRRm. J Clin Oncol [Internet. 2024;42(4).

12. Hussain MHA, Kocherginsky M, Agarwal N, Zhang J, A N. BRCAAWAY: A randomized phase 2 trial of abiraterone, olaparib, or abiraterone + olaparib in patients with metastatic castration-resistant prostate cancer (mCRPC) with DNA repair defects. Journal of Clinical Oncology. 2022;40(16 Supplement 1).

13. Ryan CJ, Small EJ, Smith MR, Taplin ME, Js B. Abiraterone in metastatic prostate cancer without previous chemotherapy. New England Journal of Medicine. 2013;368(2):138-48.

14. Hu Z, Ye Z, Zeng H, Huang Y, Y D. Abiraterone acetate in men with metastatic castration-resistant prostate cancer and no prior chemotherapy: A double-arm, multiple-centre, phase III clinical study. Annals of Oncology. 2020;31(Supplement 4).

15. Ye D, Huang Y, Zhou F, Xie K, M V. A phase 3, double-blind, randomized placebo-controlled efficacy and safety study of abiraterone acetate in chemotherapy-naive patients with mCRPC in China, Malaysia, Thailand and Russia. Asian Journal of Urology. 2017;4(2):75-85.

16. Beer TM, Armstrong AJ, Rathkopf DE, Scher HI, L Y. Enzalutamide in metastatic prostate cancer before chemotherapy. New England Journal of Medicine. 2014;371(5):424-33.

17. Pu YS, Ahn H, Han W, Huang SP, Hc W. Enzalutamide in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer: An Asian Multiregional, Randomized Study. Advances in therapy. 2022;39(6).

18. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika. 1982;69(1):239-41.

19. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515-26.

20. Kiefer C, Sturtz S, Bender R. Indirect Comparisons and Network Meta-Analyses. Dtsch Arztebl Int. 2015;112(47):803-8.

21. National Institute for Health and Care Excellence. Olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [ID3920]: Committee Papers 2023. Available from: https://www.nice.org.uk/guidance/ta951/documents/committee-papers.

22. Pfizer. Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]: Document B, company evidence submission. 2024.

23. Joint Formulary Committee. British National Formulary 2024. Available from: https://bnf.nice.org.uk/.

24. Drugs and pharmaceutical electronic market information tool (eMIT) GOVUK. 2024.

25. National Health Service. National Schedule for NHS costs. 2021.

Appendix A – Errors and unjustified changes in the model

Unjustified changes

- NHS cost code SA04L was removed from Anaemia calculations in the revised models
- NHS cost codes SA08G, SA08H AND SA08J for leukopenia were removed in the revised model although not used in the original model
- NHS cost codes from SA35A to SA35E for leukopenia were removed in the revised model although not used in the original model
- Adverse Events & costs sheet: Cell D34 (incidence of thrombocytopenia) was incorrectly linked to cell C15 rather than cell C20

Tornado coding error

- **Before**: Set parng = Application.InputBox(prompt:=prom, Title:=titl, Default:="$C$10:$C49$" & No_of_Param, Type:=8)
- **After**: Set parng = Application.InputBox(prompt:=prom, Title:=titl, Default:="$C$10:$C$54", Type:=8)

- **Before**: Set torng = Application.InputBox(prompt:=prom, Title:=titl, Default:="$H$5:K" & m + 4, Type:=8)
- **After**: Set torng = Application.InputBox(prompt:=prom, Title:=titl, Default:="$J$9:$M$57", Type:=8)

Tornado Diagram range error

- **Before**: ='Tornado data'!$K$10:m50
- **After**: ='Tornado data'!$J$8:$L$54

Single Technology Appraisal

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 12 June 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Relevant comparators were not assessed in the submission

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.3, Page 16 "It was not clear to the EAG's clinical experts what subgroup of people with mCRPC could be offered olaparib with abiraterone but could not be offered enzalutamide, or abiraterone." **Section 2.3.5, Page 27** "However, it was not clear to the EAG's clinical experts what subgroup of people with mCRPC could be offered olaparib with abiraterone but could not be offered enzalutamide." **Section 4.2.4, Page 84** "It was also consistent with clinical advice to the EAG that there is no distinct population eligible for olaparib with abiraterone but not for the other treatments included in the scope. As a result, a recommendation for people in whom olaparib with abiraterone "would otherwise be offered" is clinically invalid."	The company requests that the EAG removes or rephrases these statements as there is a subgroup of people where the PARPi and ARPi combination would be deemed more appropriate than ARPi monotherapy. Therefore, there is a distinct population eligible for olaparib with abiraterone but not for the monotherapies.	Whilst all ARPi naïve patients could be offered either enzalutamide or abiraterone monotherapy in 1st line mCRPC, the data from both TALAPRO-2 and PROpel trials (ITT results, as well as the efficacy signals in both HRRm and non-HRRm/ unknown subgroups) support the consideration of adding a PARPi to ARPi monotherapy to all patients who have not had an ARPi in the mCSPC setting and are clinically suitable for a PARPi. In addition, based on UK clinical expert opinion, the company believes that there is an important clinical need to have a choice of PARPi + ARPi combinations that have different ARPi backbones. When it comes to ARPi monotherapy, clinicians have a choice of ARPi, and there are distinct patient characteristics which would contraindicate either	The EAG does not consider this to be a matter of factual inaccuracy. In the company's justification for the amendment, they confused eligibility of people for the interventions with the relative effectiveness of the interventions. There may be differences in efficacy between the ARPi monotherapy and PARPi and ARPi combination therapy but, at the time of writing, ARPi naïve people with mCRPC were eligible for enzalutamide monotherapy, abiraterone monotherapy, or olaparib with abiraterone. Therefore, those were the relevant comparators. The EAG did not disagree with the company's comment that it would be beneficial for clinicians to have different PARPi+ARPi combination therapies that could be offered based on a person's distinct characteristics. Indeed, the company states, quite rightly,

		abiraterone or enzalutamide use. Currently, when it comes to combination therapies this choice of ARPi backbone is not available, meaning patients for whom abiraterone is contraindicated are unable to access a PARPi + ARPi combination. Therefore, the company believes that the recommendation of talazoparib plus enzalutamide for people in whom olaparib plus abiraterone would otherwise be offered is clinically valid.	that there are people for whom either abiraterone or enzalutamide are contraindicated. However, this did not support removing ARPi monotherapies as comparators. For example, in people for whom abiraterone was contraindicated, the treatment options would be talazoparib with enzalutamide or enzalutamide monotherapy. In sum, the EAG does not consider the company have provided a valid argument why ARPi monotherapy is not a treatment option for people who are ARPi naïve, or that differing patient characteristics support removing ARPi monotherapies as comparators. No changes have been made to the report.
Section 6.1.3. Page 124 **Section 6.3.3. Pages 133**	We request the EAG reconsider the selection of abiraterone monotherapy as a relevant comparator. We also strongly believe the naïve cost-effectiveness comparison between talazoparib with enzalutamide versus abiraterone is not appropriate for	Based on information included in the point above, we do not believe abiraterone monotherapy (nor enzalutamide monotherapy) is an appropriate comparator for talazoparib with enzalutamide in mCRPC. The EAG's naïve cost-effectiveness comparison	The EAG considered abiraterone monotherapy to be a relevant comparator as it sat at the same place in the current treatment pathway for people with newly diagnosed mCRPC as enzalutamide monotherapy and olaparib with abiraterone. This

	decision-making and should be removed from the report.	between talazoparib with enzalutamide versus abiraterone is fundamentally flawed as it relies of the assumption that abiraterone is clinically equivalent to enzalutamide. In TA951, "The EAG identified several recent studies in their updated evaluation of the real-world studies, and also performed a meta-analysis; the resulted in a HR of 0.84 (95% CI: 0.77 to 0.91), favouring enzalutamide [over abiraterone]." Moreover, recent RWE suggests that in chemotherapy-naïve mCRPC population, first line abiraterone was associated with worse OS versus enzalutamide in the overall population and among subgroups with older age and comorbidities.[1]	was expanded on in Sections 2.3.5 and 2.4.2 of the EAR. The EAG has explored scenario analyses investigating the impact of differential effectiveness of abiraterone and enzalutamide and the impact on cost-effectiveness conclusions in response to the FAC. See Sections 6.2.9 and 6.4 of the EAR.

Issue 2 Uncertainty related to the ITCs presented

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.4, page 17:	The company requests that the EAG rephrases these statements as it	While the company acknowledges the uncertainty in	The EAG does not consider this to be a

"Therefore, each of the ITCs submitted offered a different estimate of effect for the efficacy of talazoparib with enzalutamide versus olaparib with abiraterone for rPFS and OS, and each had substantial uncertainty/flaws. The EAG considered the unanchored MAIC to be the most appropriate ITC." "Given the uncertainty in the comparison with olaparib with abiraterone the EAG considered the demonstration of cost effectiveness versus enzalutamide to be critical to validate the plausibility of results. This comparison was not subject to the same level of uncertainty as head to head data were available." **Section 3.3.2.6, page 75:** "In sum, the EAG did not consider the results of the unanchored MAIC to be robust and were subject to substantial uncertainty." **Section 3.4.3, page 78:**	considers the current wording to be misrepresentative of the evidence base.	the ITC methodologies, it is misrepresentative to state that the ITCs had "substantial uncertainty/ flaws." The company would like to reiterate that the different ITC methodologies demonstrated consistent findings, highlighting that talazoparib with enzalutamide is generally similar or numerically more effective than olaparib with abiraterone. In addition, talazoparib with enzalutamide is dominant versus olaparib with abiraterone when any of the ITC options are selected in the cost-effectiveness model. This consistency of results from different methodologies provides confidence in the relative effectiveness of talazoparib with enzalutamide compared with olaparib with abiraterone. Given that all ITCs demonstrate that talazoparib with enzalutamide is similar or numerically more effective versus olaparib with abiraterone, and that TA951 showed that olaparib with abiraterone is cost-effective versus monotherapy	matter of factual inaccuracy. The EAG took expert statistical advice in drafting the report and have stated the causes of the uncertainty in the analysis, and the flaws in the analysis. No changes have been made to the report.

"The company presented three ITCs in the CS. Each were subject to substantial limitations as summarised in Key Issue 2. As noted, the EAG considered the unanchored MAIC to be the most appropriate ITC presented, however, it would also be useful to compare the results of each." **Section 3.5, page 79:** **"**The EAG still favoured the MAICs over the PH NMAs and FP NMAs but were aware of the substantial uncertainty linked to the results.**"** **Section 6.5, page 134:** "Each of the ITCs submitted offered a different estimate of effect for the efficacy of talazoparib with enzalutamide versus olaparib with abiraterone for PFS and OS, and each had substantial uncertainty/flaws. The analysis was relatively sensitive to which estimate which used in part due to differences in relative effect but also due to the unweighted population		with enzalutamide or abiraterone, the company considers there to be sufficient evidence for the NICE committee to make a decision on the cost-effectiveness of talazoparib with enzalutamide versus olaparib with abiraterone, which is the key comparison relevant to this appraisal. The company therefore considers it misrepresentative to state that the comparison with enzalutamide is critical as there is sufficient evidence to assess talazoparib with enzalutamide versus olaparib with abiraterone.	

providing less favourable estimates of absolute survival compared to the MAIC weighted population"			

Issue 3 Assumption that time on treatment is equal to rPFS for olaparib with abiraterone but is lower for talazoparib with enzalutamide

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, page 18: "In the EAG base case we assume that the relationship between TTD and rPFS observed for talazoparib applies to olaparib and that the relationship between TTD and rPFS observed for enzalutamide applies to abiraterone. We present scenario analysis assuming TTD is equal to rPFS" **Section 4.2.6.3, page 102:**	The company requests that the EAG rephrases these statements as it considers the current wording to be misrepresentative of the evidence base.	The company acknowledges the uncertainty and issues with the existing TTD methodology and sources in the company model but believe that the EAG approach to TTD is arbitrary and introduces other uncertainties. For the olaparib with abiraterone TTD curve, the EAG use a different methodology to estimate TTD for the olaparib arm and abiraterone arm, which includes some inconsistencies and potential biases: • For the olaparib arm and abiraterone arm TTD, time-varying	As stated in the EAG report we assume that the relationship between TTD and rPFS for olaparib as part of the combination resembles talazoparib as part of the combination and that the relationship between TTD and rPFS for abiraterone as part of the combination resembles enzalutamide as part of the combination. Details of the calculations in Excel are provided below to demonstrate this. **EAG base case** First the cumulative hazard is calculated (column AD) using the h(t) for talazoparib in Sheet Calcs - OLA + ABI from using Column L (labelled TTD talazoparib). Next the instantaneous hazard is calculated (column AE). Then the tala+enza rPFS curve is taken (from column F to column AF). The multiplier is then calculated by dividing the instantaneous hazard for TTD by the instantaneous hazard for rPFS in column

"In the EAG base case we assumed that the relationship between TTD and rPFS observed for talazoparib applied to olaparib and that the relationship between TTD and rPFS observed for enzalutamide applied to abiraterone." **Section 6.2.1, page 123:** "The TTD curve for olaparib was derived by scaling the olaparib rPFS curve using the TTD:rPFS ratio from talazoparib, while the TTD curve for abiraterone was derived by applying the enzalutamide TTD:rPFS ratio to the abiraterone rPFS curve. This allowed for treatment-specific estimates of TTD that remain consistent		HRs are applied. The time-varying HR for olaparib is calculated using the talazoparib with enzalutamide TTD values, but for the abiraterone arm it is calculated using the talazoparib only TTD value, which is inappropriate. When determining the time varying HR for each arm, it is misplaced to consider the dual combination in one arm but not the other. • For the HR scenario analysis, the proportional hazards fixed-effect NMA rPFS HR of olaparib with abiraterone vs talazoparib with enzalutamide is used. As flagged by the EAG and the company, the FE NMA analysis was considered uncertain due to the violation of the PH assumption,	AG. For OLA + ABI we take the adjusted rPFS from column K and calculate the cumulative hazard column AH, then we calculate the instantaneous hazard (column AI), then apply the multiplier from column AG to get the hazard for TTD (column AJ), then calculate cumulative hazard (column AK), then the survivor function (column AL). For enzalutamide we follow the same process taking the TTD curve for enzalutamide from column M and rPFS for tala+enza from column F to calculate the multiplier (see columns AM – AP). For abiraterone we take the OLA + ABI adjusted rPFS from column K again and apply the multiplier and recreate the survivor function – see columns AQ to AU. In the EAG base case we take the TTD for ola from column AL and for abi from column AU (as shown in the formula in Column AV and AW). The EAG noticed while cross-checking the formula that the correct formula in the top row of column AW had not been copied down. This has now been amended and the results updated. **Scenario analysis using NMA HR** In Column S in Sheet Calcs - OLA + ABI we apply the

with the clinical relationship observed between TTD and rPFS in **TALAPRO-2**." **Section 6.5, page 134:** "Assumption that TTD = rPFS for olaparib with abiraterone and not talazoparib with enzalutamide which did not align with the prior NICE or CADTH appraisal for olaparib with abiraterone"		so may not be the most appropriate approach for estimating TTD. In addition, this HR was for the olaparib with abiraterone arm in the FE NMA but has been applied only for TTD to the abiraterone arm and a different methodology is applied for the olaparib arm. The company notes that the EAG's clinical expert suggested that "in real-world practice they would not expect much difference between TTD and rPFS." The company therefore suggest a more appropriate alternative to the existing TTD methodology would be to set TTD equal to rPFS in both the talazoparib with enzalutamide and olaparib with abiraterone arms**.** This would help to address the key issued raised by the EAG (the use of unweighted	HR from the EAG-preferred company NMA in the original CS ([redacted]) to the joint tala+enza TTD to derive olaparib+abiraterone TTD. Adjustments to prevent curves are then performed in columns T and U. In Column AV, AW The EAG noted that this scenario was not being pulled through correctly to the individual TTD curves in columns AV and AW during FAC and have now corrected this and updated the results. **Scenario analysis assuming TTD = rPFS** This scenario is already presented in the EAG report. The EAG consider this a reasonable alternative way of addressing the issue but also acknowledge limitations in that treatment costs are likely to be overestimated for all treatments. [redacted]

		data alongside MAIC outcomes) and would ensure consistency of assumptions across both arms. We used the EAG corrected model (with incremental cost and QALYs being [redacted] as presented in Table 3 in the EAG report) to conduct this scenario analysis (one of EAG's existing scenario analysis "TTD equal to rPFS") and the incremented cost and QALYs are [redacted] respectively, with talazoparib with enzalutamide dominating olaparib with abiraterone.	
Section 4.2.3.6, Page 98: "The CADTH appraisal referenced did not provide the relevant TTD data"	The company also requests to remove the text *"The CADTH appraisal referenced did not provide the relevant TTD data"* on Page 98.	As presented in Table 15 of the company addendum, for olaparib with abiraterone arm in the PROpel study, published time to discontinuation data (from Page 107, Table 17 in Appendix 4 in the olaparib CADTH reimbursement review) are very close to published rPFS data (from	Thank you for pointing us to the source of the TTD data in the CADTH review. The CADTH report indicates that time on treatment data were supplied for datacut off 3 ("Clinical efficacy parameters used to characterize olaparib plus abiraterone and abiraterone, including OS and rPFS, were derived from the final analysis of the PROpel trial (DCO3), using the October 12, 2022"; page 81) whereas the rPFS data quoted by the company from Clarke et al 2022 is from data cut off one (30th July 2021) as noted

		Clarke et al. 2022[2]) with 12 months percentages of time to discontinuation for olaparib and rPFS for olaparib with abiraterone being 74.0% and 73.7%, respectively, and 24 months being 51.0% and 53.8%, respectively, supporting the company's base case assumption that time to discontinuation is the same as rPFS for olaparib with abiraterone. With EAG's preferred base case assumption to adjust time to discontinuation for olaparib with abiraterone, the derived percentages of time to discontinuation for olaparib are [redacted] at 12, 24, and 36 months, respectively, which are significantly below the reported 74.0%, 51.0%, and 47.0% at 12, 24, and 36 months, respectively, (olaparib CADTH reimbursement review) showing a lack of face	in response to clarification C1. This is therefore not a like for like comparison. The CADTH modelled base case for TTD reports a median TTD of 2.3 years with landmark discontinuation percentages of 75%, 54% 40%, 25%, 10%, 5%, 3% at 1, 2, 3, 5, 10, 15 and 20 years. Unfortunately, the same data is not reported for rPFS barring that landmark rPFS at 15 years is 12% and at 20 years is 7%. This demonstrates clearly that CADTH assume a lower TTD compared to rPFS. The report has been updated to include the relevant data from the CADTH appraisal. Finally, the EAG note that naively comparing TTD data from PROpel with modelled projections is unlikely to be informative.

		validation against published data.	

Issue 4 Assumptions made post progression

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, Page 19: "The EAG uses a constant utility value for the post progression state in the absence of a robust recent source for utilities in palliative care." "This is not in line with TA951 which assumed a much higher utility for the entire post progression state ([redacted]) or the majority of previous literature (a recent literature review found health-state utility values of 0.65 – 0.715)." **Section 2.4.2, Table 5, Page 36:** "In addition the analysis used a combination of utilities for post-progression survival	The company requests that the EAG removes or rephrases these statements as it would not be appropriate to apply the same utility for patients in second-line treatment as for patients in palliative care.	Applying separate utility values for patients in palliative care is an accepted practice in NICE technology appraisals in prostate cancer, including in TA377, TA391, and TA712. In each of these appraisals, the final palliative care utility value was lower than [redacted]. In TA377 and TA391, the final EAG and NICE Committee base case included a palliative care utility value of 0.50 and 0.62, respectively. In TA712, the final EAG and NICE Committee base case included a utility value of 0.53 for patients on fourth-line therapy. Additionally, utility values were validated by UK clinical experts who agreed that there will be a decline in utility value from initial progression free state to initial post progression state, where	The EAG does not consider this to be a matter of factual inaccuracy. The EAG notes that the company did not present direct trial-based evidence to support a distinct utility value for palliative care. The two utility values used to represent both post-progression and palliative care states are sourced from TA377 (2015), which itself relied on earlier sources, including a 2004 study, from which a utility of 0.526 was reported and subsequently rounded down to 0.500 in the model, and a 2012 study. In the absence of directly elicited utility values from

which included non-reference case sources." **Section 4.2.6.4, Page 104** **"**EAG base case: assumed one utility value for the entire progressed disease state in line with TA951" **Section 4.2.7.1, Page 107:** "The EAG used one utility value for the entire post progression state and does not apply a separate value to patients receiving palliative care." **Section 6.2.2, Table 42**		most patients are still fit enough for another oncological therapy. However, a more significant decline is expected once in the palliative care state, where patients are no longer fit enough (or have no further options) for oncological therapy. They now have a terminal disease with increasing symptoms requiring medical intervention, and deteriorating function requiring social care and potential hospital/hospice admissions before entering the death health state. Therefore, having the same utility value for both the post progression, and the palliative care health state is not reflective of the natural history of prostate cancer and applying the same utility value for patients in palliative care is an overestimate of the quality of life of those patients.	the company's trial, and given the limitations and uncertainty in the external values used, the EAG preferred to adopt an approach consistent with that used in TA951, the latest relevant prior appraisal (2024).

Issue 5 Real-world use of PARP inhibitors may be limited to people with HRR deficient tumours

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.6, Page 20	The company requests that the EAG removes or rephrases these statements	The company believes that the expert opinion sought by the	The EAG does not consider this to be a matter

“The EAG’s clinical experts stated that in their practices, olaparib with abiraterone was only offered to people with HRR deficient tumours and they expected to do the same with talazoparib with enzalutamide, if a NICE recommendation were made.” **Section 3.5, Page 80** “Olaparib with abiraterone was only offered to people with HRR deficient tumours in their practices and they expected to do the same with talazoparib and enzalutamide if a positive recommendation were made.” **Section 2.3.4, Page 27** “However, despite the proposed synergistic effect the EAG’s clinical experts stated that it was unlikely PARP inhibitors would be offered to people with HRR non-deficient tumours in their practices."	as without clarification or context these statements are misleading.	EAG are not reflective of the opinion of the wider prostate cancer community within the UK. The EAG’s statements fails to acknowledge that both olaparib with abiraterone and talazoparib with enzalutamide are licensed in the all-comers population. In addition, TA951 recommends olaparib with abiraterone, for use in the NHS for patients with and without HRR-deficient tumours. As highlighted in the CS (section B.3.7 page 44) TALAPRO-2 demonstrated that talazoparib with enzalutamide had a statistically significant rPFS benefit vs placebo with enzalutamide in people whose tumours were HRR-deficient, people whose tumours were HRR non-deficient/unknown, and in the all-comers population. PROpel demonstrated a similar benefit for olaparib plus abiraterone vs placebo plus abiraterone in both HRRm and non-HRRm patients. UK clinical experts consulted by the company did acknowledge that a stronger benefit is seen in	of factual inaccuracy. The EAG reported statements made by both of the clinical experts recruited for this project. The EAG understood these to be an important insight into the use of PARPi+ARPi combination therapy, as it stood at the time of writing, and how it might stand after the appraisal. The company’s justification for removing these statements from the report noted the clinical evidence in TALAPRO-2 for the HRR deficient / HRR non-deficient subgroups. However, these data were presented and discussed in the EAR. The EAG understood the expert’s input in Key Issue 5 to represent physician’s understanding that PARPi treatment are effective in tumours with HRR deficiency. This understanding is reflected in NICE guidance, for

		HRRm patients, however, the majority of the clinicians considered that the efficacy benefit seen in the all-comers population, and the non-HRRm subgroups cannot be excluded, and therefore access should not be restricted. Currently, there is only access to BRCA1/2 testing, whereas PROpel and TALAPRO-2 included a wider gene mutation panel and efficacy benefit was seen in non-BRCA HRRm patients that HCPs cannot test for. In addition, testing failure rates are very high in the UK as very old archival samples from initial diagnosis need to be used. Therefore, in the current testing landscape, patients with non-BRCA mutations cannot be tested for, and patients with a BRCA mutation may be missed because of poor tissue available for testing. Having the option for access in all-comers will mean the HCP can make a clinical decision about whether they feel the patient may have a HRRm that was not detected (e.g. strong family history, young age of diagnosis, very aggressive	example, in TA962 olaparib was recommended for people with BRCA mutation-positive (HRR deficient) ovarian cancer. The EAG considered it important to note the implications of how physician's understanding of PARP inhibitor efficacy may be applied in the real-world. No changes have been made to the report.

		disease responding poorly to treatments), and offer them a choice of PARPi+ARPi combination.	

Section 1.6, Page 20 "However, the EAG did not find evidence suggesting a synergistic effect between the therapies in subgroup analysis of rPFS in people whose tumours were HRR deficient and people whose tumours were non-deficient/unknown in TALAPRO-2 (3.2.3.2)." **Section 3.5, Page 80** "The company appeared to be aware of this and noted research on a proposed synergistic effect between ARPis and PARP inhibitors (Sections 2.3.4). However, the EAG did not find adequate evidence had been presented to substantiate the proposed synergistic effect between PARP inhibition and ARPis (Section 3.2.3.2)."	The company requests the EAG remove mention of an inadequate synergistic effect between ARPis and PARPis.	Clinical expert advice to the company during this appraisal, and clinical expert and committee comments during TA951, highlight the combined antitumour effect of NHT+PARPi combinations in non-HRR deficient populations. This was accepted by the committee during the TA951 appraisal. Section 1 in the company addendum details impact of talazoparib with enzalutamide on rPFS and OS outcomes. In TA951 it is mentioned that: "The clinical experts and EAG agreed that olaparib's mechanism of action is different when combined with a novel hormonal agent compared with when used alone. This is because the combination causes an interaction between the androgen receptor pathway and DNA repair pathway. This means that novel hormonal agents may enhance the effect of olaparib in tumours without the BRCA mutations and olaparib may augment the effectiveness of	The EAG does not consider this to be a matter of factual inaccuracy. The EAG assessed the evidence for a synergistic effect between ARPis and PARP inhibitors in people with HRR non-deficient tumours in Cohort 1 and Cohort 2 of TALAPRO-2 and presented the assessment in the EAR. No changes have been made to the report.

		novel hormonal agents. Prostate Cancer UK and the clinical experts agreed that people without the BRCA mutation, including those with non-BRCA HRR mutations, also get important benefits from treatment with olaparib and abiraterone. ”	

Factual inaccuracies and unclear statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.5, Page 18: “The company assumes the TTD is considerably lower than rPFS for talazoparib with enzalutamide resulting in a reduction in drug cost for talazoparib of [redacted]	The company requests that the EAG rephrases this statement to clarify that it is not only the cost of talazoparib but talazoparib with enzalutamide. Revision suggestion: “The company assumes the TTD is considerably lower than rPFS for talazoparib with enzalutamide resulting in a reduction in drug cost for talazoparib with enzalutamide of [redacted]	The original text is unclear.	Amended
Section 1.5, Page 18: “On top of the EAG-corrected base case the difference in costs when only the talazoparib discount is included reduces from	The company requests that the text is updated to: “On top of the EAG-corrected base case the difference in costs **between talazoparib with enzalutamide and olaparib with abiraterone** when only	The original text is unclear.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
[redacted]	the talazoparib discount is included reduces from [redacted]		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4.2, Page 78: "The EAG regarded this as not ideal, given it could not trace the provenance of some of the OS relative effect estimates cited"	The company requests the EAG to remove the text "*given it could not trace the provenance of some of the OS relative effect estimates cited".*	The three constant OS hazard ratios used in the economic analysis for responses to clarification question A6 were all updated indirect treatment comparison analyses based on the TALAPRO-2 final data cutoff 3rd September 2024.	No amends made as this updated analysis was not submitted for critique.
Section 4.2.6, Page 87: "…and a constant hazard ratio for OS due to lack of convergence of the FP NMA models ([redacted]; no information provided on how this was calculated and the NMA HRs do not match previous information provided)."	The company also requests the EAG to replace the text on Page 87 with more accurate and complete description: *"…and constant hazard ratios for OS due to lack of convergence of the FP NMA models ([redacted] for olaparib with abiraterone over talazoparib with enzalutamide as preferred option based on MAIC using the final data cutoff 3rd September 2024; [redacted] as other options based on fixed-effects and random-effects NMA, respectively, using the final data cutoff 3rd September 2024)*	The clearer definition of these hazard ratios (i.e. olaparib with abiraterone over talazoparib with enzalutamide) should be added to be more accurate.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.4.3.1, Page 78: "In the company's chosen solution, the HR [redacted] after about 18 months. Other solutions offered less optimistic HRs, with p=0 demonstrating continued reduction of the HR over the time horizon."	The company requests the EAG replace the text with a more accurate and complete description: *"In the company's chosen solution, the HR for* ***olaparib with abiraterone over talazoparib with enzalutamide*** [redacted] *after about 18 months. Other solutions offered different shapes of HRs over time, with p=0 demonstrating continued reduction of the HR over the time horizon."*	We propose to add "*for olaparib with abiraterone over talazoparib with enzalutamide"* to make it clearer the hazard ratios presented for fractional polynomial models have different reference treatment arm vs. the constant hazard ratios presented earlier in the same paragraph.	Thank you for the correction. The EAG have updated in line with the company's suggestion

Section 1.4, Page 17: "A suitable model was found for rPFS. It had the lowest DIC (p = -1) but was also the most optimistic, and …" **Section 3.4.2, Page 77-78:** "The fit that had the lowest DIC (p = -1) was also the most optimistic, and …" **Section 4.2.6, Page 87:** "In response to clarification question A6 the company submitted an economic analysis which used a fractional polynomial model for rPFS (p = -1, most optimistic of the 3 options presented) and …"	The company requests the EAG to remove the statements that first-order rPFS fractional polynomial model with p=-1 being the most optimistic.	Three first-order rPFS fractional polynomial models (p=-1, p=-0.5, and p=0) were deemed plausible and included in the economic analysis to respond to clarification question A6. The model with p=-1 provided the best statistical fit to the data (i.e. lowest DIC) among the three options and therefore deemed the most appropriate. Unlike constant hazard ratio, it is not straightforward to compare time-varying hazard ratios derived from fractional polynomial NMA. In this case, the implied time-varying hazard ratios (olaparib + abiraterone vs. talazoparib + enzalutamide) cross over time and are higher for fractional polynomial model with p=0 vs. p=-1 before roughly [redacted] and lower after [redacted] (see Figure 7 in our responses to clarification	Thanks for your comment. This has been amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		question A6). Therefore, it can be argued the fractional polynomial model with p=-1 is less optimistic vs. p=0 before [redacted] and more optimistic after [redacted], but a general statement that the model with p=-1 is most optimistic is inaccurate as this is not true for all values of t=time. Fractional polynomial model with p=-1 is also associated with lower incremental net monetary benefit for talazoparib with enzalutamide vs. olaparib with abiraterone vs. p=0 ([redacted]) using the model we submitted for responses to clarification question A6, meaning it is less optimistic regarding cost-effectiveness results vs. p=0.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2.8, Page 44: “Discontinuations of either treatment in each arm due to a global deterioration of health were higher in the talazoparib with enzalutamide arm than the placebo with enzalutamide arm ([redacted] versus [redacted]).“	The company requests that this statement is deleted or replaced.	The values [redacted] and [redacted] were obtained by taking the average of the proportions of patients discontinuing individual treatments in each treatment arm. The company believes that this approach is an oversimplification and risks misinterpretation for the reader. The company suggests that the EAG instead considers the proportion of patients discontinuing individual treatments in each treatment arm: “Discontinuations due to a global deterioration of health were higher in the talazoparib with enzalutamide arm (talazaporib: 17.1%, enzalutamide: 18.3%) than in the placebo with enzalutamide arm (placebo: 15.0%, (enzalutamide: 15.2).”	Thank you for the correction. The EAG have updated in line with the company’s suggestion.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		The company also suggests that the EAG consider the proportion who discontinued due to progression.	
Section 3.2.3.1, Figure 4, Page 50: "Figure 1: Overall survival in all patients (adapted from Figure S2 in Agarwal et al. 2023)[3]"	The company requests that the text is updated to: "Figure 2: Overall survival in all patients **in Cohort 1 of TALAPRO-2** (adapted from Figure S2 in Agarwal et al. 2023)[3], data cutoff: August 16th 2022"	The original text misreports the population from which the data used to generate the curve was obtained.	Thank you for the correction. The title of the table has been edited in-line with the company's suggestion.
Section 3.2.3.4, Page 54: "The mean duration of enzalutamide treatment was [redacted] weeks in the talazoparib arm and [redacted] in the placebo arm."	The company requests that the text is updated to: "In the August 16th 2022 data cutoff, the mean duration of enzalutamide treatment was [redacted] weeks in the talazoparib arm and [redacted] in the placebo arm."	Factual inaccuracy in the rounding of the mean duration of the placebo arm.	Thank you for the correction. The mean duration of the placebo arm has been edited to match the company's suggestion.
Section 3.3.2.5, Page 73: "The primary MAIC analysis (adjusted for primary factors and stratification factors) found	The company requests that the text is updated to:	The original text misreports the p-value. The p-value should also be underlined	Thank you. The p value has been edited to match

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
talazoparib with enzalutamide had a [redacted] olaparib with abiraterone for OS (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted])."	"The primary MAIC analysis (adjusted for primary factors and stratification factors) found talazoparib with enzalutamide had a [redacted] olaparib with abiraterone for OS (HR: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted])."	and highlighted blue to indicate CIC.	the company's correction.
Section 4.2.6, Page 85: "The company used dependent models in the Excel file. The EAG sought clarification on this and the company confirmed the intention was to select unstratified curves (response to clarifications sent 2nd May 2025, question 2). No rationale was provided for this and the EAG was uncertain of the validity of this given that proportional hazards was not deemed appropriate in the unweighted analysis, particularly for OS (See Section 3.3). The EAG requested additional clarification (response to clarifications sent 20th May 2025). The company did not justify the use of unstratified models and instead stated that the EAG's interpretation of the company's presentation of different AIC/BIC statistics per arm was incorrect. The EAG did not see how the company's assertion could be the case. AIC is calculated as 2 * number of parameters – 2 * the maximum value of the likelihood function for the model. Unstratified means that one model is fitted to the two groups	The company requests that the EAG removes or rephrases these statements as the company presents a stratified analysis.	In both modelled comparisons presented by the company, independent models were fitted to each treatment arm, allowing curves for outcomes and comparators to be selected separately, as opposed to utilising a hazard ratio. This was done in part to address concerns that the proportional hazards assumption was not appropriate. In the modelled comparison to olaparib with abiraterone, seven parametric curve options are presented in the model for both OS and rPFS, modelled independently for each treatment arm. The	Thank you for the clarification. the EAG would like to note that this is a result of the company mislabelling the data used for curve fitting in the company base case in both the 'Model Mechanics' and 'Wei_MAIC' sheets for OLA+ABI and TALA+ENZA. EAG report has been updated.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and therefore only one likelihood function exists. The implication of this is that the fit statistics presented did not relate to the unstratified analysis used in the economic model. The EAG therefore remained concerned that the survival analysis fit statistics are inconsistent with the economic model, that independent curve fits (which TSD14 generally prefers) were not provided in the Excel file and that unstratified models have been inappropriately selected with no justification provided." **Section 6.2.7, Page 126** "We could not test the impact of using stratified curves in the comparison to olaparib with abiraterone in line with the company's original stated intention in the CS addendum and the goodness of fit statistics provided in their clarification response. We therefore tested the unstratified generalised gamma, log-logistic and lognormal curves as the best fitting options according to statistical fit criteria and comparison to TA951 for olaparib with abiraterone. In the comparison to enzalutamide we selected the gamma curve in the EAG base case as this better aligned with the rPFS estimates for current care from TA951 and clinical expert advice to the EAG and avoided		separate AIC/BIC statistics per arm presented for TALA+ENZA and OLA+ABI in the CS addendum and clarification response correspond to the curves presented in the model for each distribution in each treatment arm. The seven parametric curve options presented in the model, are therefore aligned with TA951 and the recommendation of NICE DSU TSD14. In the modelled comparison to enzalutamide monotherapy, seven parametric curves are similarly presented for both OS and rPFS. In this model, the AIC/BIC values for each treatment arm are presented together, which is suitable as the comparator selection (enzalutamide) is present in both treatment arms. It should be noted that despite the setting	

the issues with the OS and rPFS curves crossing early on in the time horizon." **Section 6.5, Page 135** "The company appeared to suggest that they preferred stratified curves in their CS addendum (they state independent fits were preferred) and supplied separate AIC / BIC statistics per arm in the comparison to olaparib with abiraterone which would align with this but in their model provide only unstratified curves (stratified curve parameters were the same for both arms and were therefore assumed to be placeholders). The EAG did not consider the use of unstratified curves to be reasonable given that proportional hazards appeared unlikely to hold within TALAPRO-2, particularly for OS. The EAG therefore noted uncertainty around the survival curves selected although the landmark estimates appeared broadly plausible when compared to TA951. This uncertainty was, however, limited as the treatment effect modelled was generally limited to the observed trial period (hazard ratio tending to 1 either during or shortly after the trial)."		applying for both arms, different trial data is sourced for each arm i.e., enzalutamide TTD data is collected separately for the patients in the talazoparib with enzalutamide arm, and the enzalutamide and placebo arm. The company's analysis can therefore be termed 'stratified' as the different treatment arms are not pooled in the survival calculations. The company notes that the presence of unused stratified curve parameters in the back sheets of the modelled comparison to olaparib with abiraterone, which "*were the same for both arms and were therefore assumed to be placeholders*", are likely the source of the misinterpretation of the analysis. These parameters were artefacts of the initial NMA-based model prior to the use of a MAIC-weighted	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		analysis with treatment arms modelled independently. In the interest of keeping to submission timelines and maintaining a pragmatic approach, the company were not able to completely remove these within the time frame of the appraisal.	
Section 4.2.6.1, Page 90 "The EAG could not see any visible kinks in the OS curves provided by the company for any of the other curve fits in Figure 6 of their response to clarification B2." "Additionally, the EAG noted that altering the OS rather than rPFS curve selection to account for issues with curves crossing was not in line with the decision taken from the weighted data." "The EAG considered the generalised gamma curve more appropriate in terms of visual and statistical fit and use this in our base case but	The company requests that the EAG removes or rephrases these statements as the company base case in the enzalutamide model presents appropriate curve selections.	The company considers the EAG's choice of the gamma distribution for rPFS in the enzalutamide model to be inappropriate as this distribution has the highest AIC/BIC values (AIC difference of ~30) and is therefore the worst statistical fit. The gamma distribution also has poor visual fit for rPFS for both treatment arms. The company also note that the	This is not a factual inaccuracy. The EAG has explained in the report the rationale for curve selection which stems in part from the need to provide a more realistic prediction for OS. This

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
note remaining limitations around the unjustified use of unstratified analysis." **Section 4.2.6.2, Page 97** "However, given that this selection results in OS and rPFS crossing relatively early on in the model which was not considered plausible the EAG preferred the gamma curve in our base case. This provides as a more conservative estimate in line with TA951 and clinical expert advice to the EAG."		EAG curve selection (OS = generalized gamma; rPFS = gamma) introduces a kink at cycle 351 in the model. These issues highlight the flaws in the EAG base case selection in the enzalutamide model. The company therefore maintains that their approach to the enzalutamide curve selection was more robust and appropriate than the EAG approach. The company considered multiple factors across both OS and rPFS to select the most appropriate curves for the enzalutamide model, including statistical fit, visual fit, comparison with TA951 and other previous appraisals, alignment with landmark survival estimates, and the avoidance of kinks in the curves. Based on this, while the company acknowledges	necessitated amends to rPFS as the companies preferred rPFS curve crosses the EAGs preferred OS curve early in the time horizon [redacted]

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		there is no clear best choice for the OS and rPFS curves due to kinks in most combinations, the log-normal distribution for rPFS and OS is a more appropriate choice than the EAG preferred curve selections as it is a better statistical fit, has no kink, and provides comparable landmark estimates to the observed KM data and TA951 values.	
Section 4.2.6.2, Page 95: "The EAG thought his was because the number of decimal points was incorrectly placed (by a factor of 100) for all curves except the generalised gamma."	The company requests the text to be updated to: "The EAG thought **this** was because the number of decimal points was incorrectly placed (by a factor of **10**) for all curves except the generalised gamma."	Typographical error in "this", and factual inaccuracy in the factor for the number of decimal points.	Amended
Section 4.2.6.3, Page 98: "The company stated that the TTD data presented in their addendum (Table 15) comes from the Clarke et al. 2022 abstract (CQ C1).	The company requests the text to be updated to: "The company **provided** TTD data presented in their addendum (Table 15) **sourced from Clarke et al. 2022. The**	The original text indicated that the data could not be identified in Clarke et al. 2022. The company, therefore, is providing	This text has been amended in response to earlier comments. The

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
This data could not be identified by the EAG in this paper."	**data was obtained by digitising Figure 1B in the Clarke et al. 2022 publication, which presents the olaparib with abiraterone BICR-assessed rPFS Kaplan-Meier curve**"	further clarification on how the data was sourced.	EAG note, however, that Clarke et al does not provide TTD data. It provides rPFS data as per the company's clarification.
Section 4.2.6.4, Page 102: "The company did not state the exact source, but we assume it was taken from Table 41 of the TA951 CS assuming that the market share post enzalutamide applies removing the possibility to use olaparib monotherapy."	The company requests the text to be updated to: "The company did not state the exact source, but we assume it was taken from Table 41 of the TA951 CS. **This assumes** that the market share post enzalutamide **involves** removing the possibility to use olaparib monotherapy."	The original text is unclear.	Amended
Section 4.2.6.3, Page 103: "The use of the number of cycles of treatment reported in the Tannock et al paper to calculate the time to receipt of palliative care was inappropriate as patients in that trial were only scheduled to receive up to 5 six weekly cycles of docetaxel."	The company requests that the text is updated to: "The use of the number of cycles of treatment reported in the Tannock et al paper to calculate the time to receipt of palliative care was inappropriate as patients in that trial **were scheduled to receive either up to 10 cycles of docetaxel administered every three**	The original text is unclear and factual inaccuracy in reporting study treatment schedules.	Thank you for this comment. Section has been updated

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	weeks or 5 six-week cycles of docetaxel administered weekly."		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.3.1, Page 25 "Clinicians are now likely to offer ARPi based treatment to people who are eligible for chemotherapy in the first line mCRPC setting." **Section 2.3.1, Page 25** Figure 1: Current treatment pathway for mCRPC **Section 2.3.5, Page 28** Figure 2: Proposed treatment pathway for mCRPC **Section 3.5, Page 79** "Clinicians are now likely to offer ARPi based treatment to people who are eligible for chemotherapy in the first line mCRPC setting."	The company believes that the treatment pathways discussed within the EAG report need clarity and contextualisation depending on what patients have had in mCSPC. Therefore, the request is to revise the diagrams and the statements for further clarity.	The treatment pathway figures presumed that a patient has not had any ARPi or chemotherapy in mCSPC, or would initially just have ADT as first line of treatment in mCRPC (which is not an appropriate treatment option by itself). However, the current standard of care in UK practice is treatment intensification in mCSPC by adding an ARPi monotherapy (enzalutamide, abiraterone or apalutamide) to ADT, or in some cases triple therapy with docetaxel+darolutamide+ADT. The majority of prostate cancer patients will not be eligible for an ARPi (or ARPI based combination) in mCRPC as they will have had one in mCSPC. There are however, a small pool of patients with mCRPC who have not had an ARPi in mCSPC, and these would include patients who had single agent docetaxel when this was standard of care (and have a very prolonged progression free	Thank you for this comment. We have edited Section 2.3.1 of the EAR to make it clear that people can be treated with ARPis in the mCSPC setting and re-treatement with ARPis, even in a further prostate cancer setting, is not permitted in the NHS.

		period) and those with more indolent disease where ADT alone was felt to be appropriate (or was the patient's choice). These patients would be eligible for ARPi monotherapy or an ARPi based combination upon progression to mCRPC.	
Section 2.3.6, Page 29, Table 4 "Talazoparib dose can be reduced stepwise down to 0.1 mg once daily due to toxicity. Dose can be reduced (120 mg or 80 mg) due to toxicity."	The company requests the EAG to add the missing the word 'enzalutamide' in the sentence - Dose **of enzalutamide** can be reduced (120 mg or 80 mg) due to toxicity.	Missing word	Thank you. The report has been edited in-line with the company's correction.
Section 2.3.6, Page 30, Table 4 "Co-administration with 160 mg enzalutamide increases talazoparib exposure approximately 2-fold."	The company requests that the EAG removes or rephrases this statement as without clarification or context this statement is misleading.	The therapeutic effect of talazoparib is seen at systemic exposure of 1mg (as is the dose in breast cancer). In the safety run in part of TALAPRO-2, it was found that co-administration of talazoparib with enzalutamide increased exposure approximately 2-fold. The dose was therefore reduced to 0.5mg – the 2-fold increase in exposure is therefore expected to bring a 1mg systemic therapeutic level and not lead to extra toxicity.	The EAG accepts the company's reasoning and has removed this statement from the report.

Section 2.3.6, Page 31, Table 4 "This combination does not require concomitant steroid treatment."	The company requests the EAG to include additional differences that may impact treatment choice to the comparison table along with the existing point on concomitant steroid use.	There are certain patient characteristics that make patients more suitable for either enzalutamide or abiraterone (and indeed there are contraindications to each ARPi). Characteristics that may preclude abiraterone include cardiovascular disease (common in elderly prostate cancer population), requirement for prednisolone (especially for patients with diabetes) and where more frequent initial monitoring would be less desirable. Characteristics that may preclude enzalutamide include cognitive impairment, where fatigue is already problematic, interactions with other medications (e.g. anticoagulants), history of seizures, or a desire to have less frequent monitoring. Based on UK clinical expert opinion, the company believes that there is an important clinical need to have a choice of PARPi+ARPi combinations that have different ARPi backbones. When it comes to ARPi monotherapy, clinicians currently have a choice of which ARPi is most suitable for their patients, and this is demonstrated by the prescribing data provided by the EAG showing	The EAG does not consider this to be a matter of factual inaccuracy. No changes have been made to the report.

		higher market share for enzalutamide than abiraterone. Currently, when it comes to combination therapies this choice of ARPi backbone is not available, meaning patients whom abiraterone is contraindicated are unable to access a PARPi + ARPi combination. Therefore, the company believes that these key differences need to be highlighted when we are comparing talazoparib plus enzalutamide with olaparib plus abiraterone.	
Section 2.4.1, Page 32 "there has been a shift from offering docetaxel to offering ARPis in the first line setting."	The company requests the EAG to revise this sentence to reflect the full context of the treatment lines, taking into account what patients will have in the mCSPC setting.	This statement is only correct if the patient has not had an ARPi in the mCSPC setting.	Edits were made to the report in response to a previous comment: "We have edited Section 2.3.1 of the EAR to make it clear that people can be treated with ARPis in the mCSPC setting and re-treatement with ARPis, even in a further prostate cancer setting, is not permitted in the NHS".
Section 2.4.2, Page 35, Table 5	The company requests the EAG to revise the wording to reflect the fact that a model with comparison to enzalutamide	An economic model comparing talazoparib plus enzalutamide with enzalutamide monotherapy was	Thank you. The EAG has edited the report in-line

"Therefore, the EAG has requested the company to include a comparison to enzalutamide within the economic model."	was provided by the company at clarification stage.	submitted by the company at clarification stage in the interest of transparency even though the company believe it is not a relevant comparator.	with the company's suggestion.
Section 3.2.3.1, Page 46 "It was unclear to the EAG why the efficacy of the comparator was different between the two cohorts given that the only difference in recruitment between the cohorts was limiting Cohort 2 to people who were HRR deficient." **Section 3.2.3.1. Page 47** **"**However, the OS in the placebo with enzalutamide arm in Cohort 2 was notably [redacted] than the placebo with enzalutamide arm in Cohort 1. While the EAG was concerned that the estimates of effectiveness in the comparator arms were [redacted] in each cohort, the EAG accepted that the efficacy of talazoparib with enzalutamide was [redacted] in Cohort 1, where 21% of	The company request the EAG to revise this section considering the prognostic impact that the HRR deficiency carries.	Whilst the only difference in recruitment between Cohort 1 and Cohort 2 was presence of a HRR deficiency, HRRm prostate cancer is more aggressive and typically has a poorer response to ARPi. The comparator arm in cohort 1 has predominantly 70-80% non-HRRm patients who respond better to ARPi, whereas cohort 2 control arm was 100% HRRm patients. This explains the difference in rPFS and OS for the control arms between cohort 1 and 2. This can be further demonstrated in the prespecified HRRm and non-HRRm/unknown subgroup analysis in Cohort 1, with the control arm in HRRm subgroup performing worse than the control arm in non-HRRm/unknown subgroup. There is increasing evidence of the prognostic significance of HRR gene alterations in patients with advanced prostate cancer. Several retrospective studies have	The EAG does not consider this to be a matter of factual inaccuracy. The EAG took a balanced approach to assessing the similarities and differences in efficacy reported for talazoparib with enzalutamide and enzalutamide monotherapy in Cohort 1 and Cohort 2. No changes have been made to the report.

participants were HRR deficient, and Cohort 2, where 100% of participants were HRR deficient." **Section 3.2.3.2, Page 53** "HRR status was not understood to be treatment effect modifier for enzalutamide and there may be other differences between the participants in Cohort 1 and Cohort 2 that influenced the treatment effect."		demonstrated that patients with germline HRR gene alterations have a shorter time to castration resistance and worse overall survival.[4,5]	
Section 4.2.6.4, Page 102 "In TA951, the experts stated that retreatment with NHA or olaparib monotherapy was not permitted in UK clinical practice following disease progression on abiraterone or enzalutamide."	The company request the EAG to revise this section to reflect the fact that as per the NICE recommendation olaparib monotherapy is an option for patients with mCRPC with BRCA mutations after progression on abiraterone or enzalutamide.	Olaparib is recommended, within its marketing authorisation, as an option for treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) in adults. (TA887)	Thank you for this clarification, amended. Scenario analysis has been added including the cost of olaparib post enzalutamide to the report in Section 6.2.10 and Section 6.4. There was a limited impact on the ICER.
Section 4.2.6.4, Page 104 "Clinical expert advice to the EAG was that the proportion of time spent in palliative care would be expected to be	For adequate clarity, the company requests the EAG to include additional detail to this section regarding the reversibility of toxicity in talazoparib upon discontinuation and is not expected to	It should be noted that, 37.4% of patients receiving talazoparib plus enzalutamide in TALAPRO-2 received a subsequent line of treatment, compared to 33% of olaparib plus abiraterone patients in	The EAG has accurately reflected the advice provided by the clinical experts we consulted

higher for talazoparib with enzalutamide relative to olaparib with abiraterone as patients receiving this combination take longer to progress and there is a higher toxicity burden with talazoparib with enzalutamide meaning that patients are likely to be less fit for further therapy once they progress.”	significantly impact fitness for further lines of treatment.	PROpel. The company acknowledges the EAG’s clinical experts concern regarding the toxicity of talazoparib plus enzalutamide, however, it doesn’t align with the trial data findings regarding subsequent therapies, hence, indicating no significant difference between the fitness profile of patients in both groups which can impact further treatment and palliative care. In addition, the ability to have further treatment tends to be limited by deterioration in performance status due to progression of disease or lack of further treatment lines.	therefore no changes have been made. In addition, when comparing the two trials 50.2% of patients in TALAPRO-2 experienced a PFS event of which 37.4% received subsequent treatment i.e. 75% of eligible patients. This compares to 54.9% experiencing a PFS event in PROpel[6] with 44.9% receiving subsequent treatment i.e. 82% of eligible patients in the final prespecified overall survival results. The EAG could not find the source of the 33% quoted by the company but assumes that this is from an earlier datacuts and notes that the proportion of eligible patients who receive subsequent treatment rather than the overall proportion is of most

			importance. Using PFS events as the denominator for this calculation is likely to represent a reasonable proxy for eligibility.
Section 4.2.8.5, Page 113 "The EAG considered this to be double counting as TA951 did not include both a palliative care cost and a terminal care cost and the types of resource use discussed as being included in the expert estimates used in that appraisal were covered within the palliative care costs presented by Round et al. 2015." **Section 6.2.5, Page 125** "The EAG base case excluded terminal care costs due to double counting with palliative care costs."	The company requests the EAG to rephrase these statements by acknowledging the palliative care need for the patient group to reflect accurate clinical practice in the disease area.	Based on the UK clinical experts inputs, the company believes that the confirmed patients will often be referred to palliative care upon diagnosis of mCRPC. As they progress through lines of treatment, the proportion of patients needing palliative care input will increase, as well as the palliative care resources needed to appropriately care for them. The clinical experts confirmed that once oncological treatment has stopped, all patients will be under palliative care with significantly higher resource use needed to manage the end of their life. Therefore, the company believes that inclusion of both a palliative care cost and a terminal care cost is not double counting but reflects the different levels of palliative care patients receive within the different health states. The differentiation	The EAG maintains that including both terminal care and palliative care costs would constitute double counting in this context, as the source used to inform the palliative care costs in the company's model estimates the cost of care during the last 12 months of life for patients with prostate cancer. By definition, this captures the trajectory of increasing healthcare resource use as patients approach the end of life. As such, terminal care costs are already factored within the broader palliative care estimate, and adding a

		between palliative care and terminal care costs has also been accepted by respective EAGs in various other oncology submissions, including TA423 (eribulin for treating locally advanced or metastatic breast cancer after two or more prior chemotherapy regimens), TA520 (atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy), and TA704 (trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies).	separate terminal care cost would lead to overestimation.
Section 4.2.7.3, Page 109 **"**Given the above the EAG did not consider the company's method for inclusion of SREs in the model to be robust and excluded SREs from the EAG base case." **Section 6.2.3, Page 125** "The EAG base case in the comparison to olaparib with abiraterone excluded skeletal related events as the EAG	The company requests that the EAG removes or rephrases these statements as it would not be appropriate to exclude SREs from the base case economic analysis.	Based on the UK clinical experts opinion, the company believes that the exclusion of SREs from the EAG base case does not appropriately reflect the effects of SREs on mCRPC patients, thus limiting the clinical relevance of the economic analysis. As noted by clinical expert advice to the EAG, "*SREs can be related to treatment (in the case of fractures particularly antigen deprivation treatment) but overall cancer (and disease progression) is the biggest contributor to these effects*". These	The EAG provide scenario analysis demonstrating the impact of including SREs using more plausible assumptions. There was no impact on the ICER to 0 decimal places compared to the EAG base case as the total costs / QALYs changed a similar amount in both arms.

did not consider the companies method for inclusion of SREs in the model to be robust.”		statements recognise the effects of SREs and therefore support their inclusion in the model base case. While the company acknowledges the EAG’s concerns regarding the application of different SRE probabilities across treatments, the exclusion of SREs from the base case lacks clinical validity. Furthermore, in TA951, SREs were accepted in the base case by the NICE committee. As TA951 was in the same indication as the current appraisal, the company believes that the omission of SREs from the EAG base case lacks consistency and clinically plausibility.	

Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 1.1, Table 1, Row 4, Page 13: “Key Issue 2”	The company requests that the text is updated to: “Key Issue **3**”	Typographical error.	Corrected.
Section 1.3, Page 16:	The company requests that the text is updated to:	Typographical error (delete “enzalutamide”).	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
“The EAG noted that enzalutamide the primary patent for enzalutamide in the UK is set to expire in 2026.”	“The EAG noted that the primary patent for enzalutamide in the UK is set to expire in 2026.”		
Section 1.4, Page 17: “This comparison was not subject to the same level of uncertainty as head to head data were available.”	The company requests that the text is updated to: “This comparison was not subject to the same level of uncertainty as head**-**to**-**head data were available.”	Typographical error.	Corrected.
Section 1.5, Page 18: “Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; ; EAG, External Assessment Group; rPFS, radiographic progression-free survival; TTD, time to treatment discontinuation”	The company requests that the text is updated to: “Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; EAG, External Assessment Group; rPFS, radiographic progression-free survival; TTD, time to treatment discontinuation”	Typographical error. Erroneous additional semi-colon.	Corrected.
Section 1.6, Page 20: “The EAG caveat this analysis with a warning that it was a naïve indirect comparison and, as such, was subject to a high risk of bias and uncertainty This uncertainty was widened by unattributable differences in comparator efficacy between the cohorts.”	The company requests that the text is updated to: “The EAG caveat this analysis with a warning that it was a naïve indirect comparison and, as such, was subject to a high risk of bias and uncertainty**.** This uncertainty was widened by unattributable differences in comparator efficacy between the cohorts.”	Typographical error. Missing full-stop.	Corrected.
Section 1.7, Page 21:	The company requests that the text is updated to:	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The cost difference between olaparib with abiraterone and talazoparib and enzalutamide increases marginally from [redacted] in the corrected company base case to [redacted] in the EAG base case."	"The cost difference between **enzalutamide monotherapy** and talazoparib **with** enzalutamide increases marginally from [redacted] in the corrected company base case to [redacted] in the EAG base case."		
Section 2.2, Page 23: "The company presented its description of mCRPC in CS Section B.1.3.1 of the CS."	The company requests that the text is updated to: "The company presented its description of mCRPC in Section B.1.3.1 of the CS."	Typographical error. Repetition of "CS".	Corrected.
Section 2.2.1, Page 23: "The CS reported that prostate cancer was the most common and most frequently diagnosed form of cancer in men in the United Kingdom (UK). It was the most common and most frequently diagnosed form of cancer in people who have prostates in the UK in 2020.[7] "	The company notes that there is repetition in the statements provided in the two sentences and suggests that one sentence is deleted.	Typographical error.	One sentence has been deleted and the other edited.
Sections 2.2.1, Page 23: "This data were true as of 2017-2019.[8]"	The company requests that the text is updated to: "**These** data were true as of 2017-2019.[8]"	Typographical error.	Corrected.
Section 2.3.1, Page 25: "People who are indicated for chemotherapy have docetaxel first line, and people who do not, receive androgen	The company requests that the text is updated to: "People who are indicated for chemotherapy have docetaxel first line, and people who **are**	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
receptor pathway inhibitor (ARPi) based treatment first line."	**not** receive androgen receptor pathway inhibitor (ARPi) based treatment first line."		
Section 2.3.1, Figure 1, Page 25: "People who are eligible for chemotherapy may instead choose to have ARPis"	The company requests that the text is updated to: "*****People who are eligible for chemotherapy may instead choose to have ARPis" "**ADT – Androgen deprivation therapy; mCRPC – Metastatic castration resistant prostate cancer."**	Typographical error (missing asterisk) and missing abbreviations.	Corrected.
Section 2.3.3, Page 26: "ADTs reduce androgen levels in the body which the cancer cells need to grow, while ARPIs further block the androgen receptor, preventing its activation and leading to cell death."	The company requests that the text is updated to: "ADTs reduce androgen levels in the body which the cancer cells need to grow, while **ARPis** further block the androgen receptor, preventing its activation and leading to cell death."	Typographical error.	Corrected.
Section 2.3.5, Figure 2, Page 28	The company requests that the text is updated to: "**ADT – Androgen deprivation therapy; mCRPC – Metastatic castration resistant prostate cancer."**	Missing abbreviations	Corrected.
Section 2.3.6, Table 4, Page 29: "Talazoparib dose can be reduced stepwise down to 0.1 mg once daily due to toxicity.	The company requests that the text is updated to:	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Dose can be reduced (120 mg or 80 mg) due to toxicity."	"Talazoparib dose can be reduced stepwise down to 0.1 mg once daily due to toxicity. **Enzalutamide d**ose can be reduced (120 mg or 80 mg) due to toxicity."		
Section 2.3.6, Table 4, Page 30: "Talazoparib with enzalutamide is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated." "Olaparib with abiraterone and prednisone is indicated in combination or prednisolone for the treatment of adults with mCRPC in whom chemotherapy is not clinically indicated."	The company requests that the text is updated to: "Talazoparib is indicated in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated." "Olaparib with abiraterone and prednisone **or prednisolone** is indicated for the treatment of adults with mCRPC in whom chemotherapy is not clinically indicated."	Typographical error (repetition of "with enzalutamide").	Corrected.
Section 3.1, Table 6, Page 38: "Records were were independently reviewed by two reviewers at title/abstract and at full text." "The company used the using the NICE Single Technology Appraisal Evidence Submission Checklist for assessment of risk of bias in RCTs."	The company requests that the text is updated to: "Records were independently reviewed by two reviewers at title/abstract and at full text." "The company used the NICE Single Technology Appraisal Evidence Submission Checklist for assessment of risk of bias in RCTs."	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2.8, page 44: "Discontinuations of enzalutamide were higher in the placebo with enzalutamide arm (84.3%)"	The company requests that the text is updated to: "Discontinuations of enzalutamide were higher in the placebo with enzalutamide arm (83.8%)"	Typographical error.	Corrected.
Section 3.2.3.1, Page 47: "The EAG assessed the proportional hazards (PH) assumption for rPFS in Cohot 1 of TALAPRO-2."	The company requests that the text is updated to: "The EAG assessed the proportional hazards (PH) assumption for rPFS in **Cohort** 1 of TALAPRO-2."	Typographical error.	Corrected.
Section 3.2.3.2, Page 52: "The EAG compared the estimates of effect for the talazoparib and enzalutamide arms of Cohort 1 (21% confirmed HRR deficient) and Cohort 2 (100% confirmed HRR deficient) for rPFS and OS in Section **Error! Reference source not found.**." "It was notable to the EAG that the estimates of effect for rPFS and OS were [redacted] in the talazoparib and enzalutamide arms in Cohort 1 (21% HRR deficient) and Cohort 2 (100% HRR deficient)."	The company requests that the text is updated to: "The EAG compared the estimates of effect for the talazoparib **with** enzalutamide arms of Cohort 1 (21% confirmed HRR deficient) and Cohort 2 (100% confirmed HRR deficient) for rPFS and OS in Section **Error! Reference source not found.**." "It was notable to the EAG that the estimates of effect for rPFS and OS were [redacted] in the talazoparib **with** enzalutamide arms in Cohort 1 (21% HRR deficient) and Cohort 2 (100% HRR deficient)."	Typographical error.	Corrected.
Section 3.2.3.2, Page 53: **"**HRR status was not understood to be treatment effect modifier for enzalutamide	The company requests that the text is updated to:	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and there may be other differences between the participants in Cohort 1 and Cohort 2 that influenced the treatment effect."	"HRR status was not understood to be **a** treatment effect modifier for enzalutamide and there may be other differences between the participants in Cohort 1 and Cohort 2 that influenced the treatment effect."		
Section 3.2.3.4, Page 57: "Skeletal related events (SREs) were reported in Section 1.32 of the Addendum."	The company requests that the text is updated to: "Skeletal related events (SREs) were reported in Section 1.3.2 of the Addendum."	Typographical error.	Corrected.
Section 3.3.1.3, Page 61: "Table 18: Summary of treatment effects vs talazoparib with enzalutamide for OS, comparison of NMA analyses (adapted from Table 7 in the cost comparison clarification response)"	The company requests that the text is updated to: "Table 18: Summary of treatment effects vs talazoparib with enzalutamide for OS, comparison of NMA analyses (adapted from Table **8** in the cost comparison clarification response)"	Typographical error.	Corrected.
Section 3.4.3.1, Page 78: "The company presented a plots of the time-varying HRs for this solution, and two other 1st order models, in Figure 7 (CQ A6)."	The company requests that the text is updated to: "The company presented plots of the time-varying HRs for this solution, and two other 1st order models, in Figure 7 (CQ A6)."	Typographical error.	Corrected.
Section 3.5, Page 79:	The company requests the text to be updated to:	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"For example, the participants in the MAIC could not matched, or the analysis adjusted, for baseline pain."	"For example, the participants in the MAIC could not **be** matched, or the analysis adjusted, for baseline pain."		
Section 4.2.1, Page 82, Table 26 "30 years at this point less than 0.1% of patients remained alive in all arms in both models."	The company requests that the text is updated to: "30 years**, at which** point less than 0.1% of patients remained alive in all arms in both models."	Typographical error	Amended.
Section 4.2.6.1, Page 90 "The EAG did not agree with the companies base case curve choice for the unweighted population (lognormal) as this had a poor statistical fit (5th best and AIC deviation of ~[redacted]) and a poor visual fit to the enzalutamide arm."	The company requests that the text is updated to: "The EAG did not agree with the **company's** base case curve choice for the unweighted population (lognormal) as this had a poor statistical fit (5th best and AIC deviation of ~[redacted]) and a poor visual fit to the enzalutamide arm."	Typographical error	Corrected.
Section 4.2.6.2, Page 95 "The EAG also noted that the more optimistic cluster crossed the companies selected OS curve relatively early on in the time horizon and when a reasonable proportion of patients remained in PFS (~[redacted])."	The company requests that the text is updated to: "The EAG also noted that the more optimistic cluster crossed the **company's** selected OS curve relatively early on in the time horizon and when a reasonable proportion of patients remained in PFS (~[redacted]).	Typographical error	Corrected.
Section 4.2.6.2, Page 97	The company requests that the text is updated to:	Typographical error	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"This provides as a more conservative estimate in line with TA951 and clinical expert advice to the EAG."	**"**This provides ~~**as**~~ a more conservative estimate in line with TA951 and clinical expert advice to the EAG."		
Section 4.2.6.3, Page 99 **"**These clearly show the bias introduced by use of unweighted data for TTD introduces non-negligible bias."	The company requests that the text is updated to: "These clearly show the use of unweighted data for TTD introduces non-negligible bias."	Typographical error (delete "bias introduced by")	Corrected.
Section 4.2.6.3, Page 100, Figure 14	The company requests that the text is updated to: Abbreviations: KM, Kaplan-Meier; rPFS, radiographic progression-free survival; TTD, time-to-treatment discontinuation	Typographical error (missing abbreviations)	Corrected.
Section 4.2.6.3, Page 100, Figure 15	The company requests that the text is updated to: "Abbreviations: PBO, placebo; rPFS, radiographic progression-free survival"	Typographical error (missing abbreviations)	Corrected.
Section 4.2.6.3, Page 102 "We present scenario analysis assuming TTD is equal to rPFS and using the hazard ratio from the original NMA for rPFS to create a proxy TTD curve for olaparib with abiraterone based upon the data for talazoparib with enzalutamide."	The company requests that the text is updated to: "We present scenario **analyses** assuming TTD is equal to rPFS and using the hazard ratio from the original NMA for rPFS to create a proxy TTD curve for olaparib with abiraterone based upon the data for talazoparib with enzalutamide."	Typographical error	Corrected

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6.3, Page 103 "Key: ALP, alkaline phosphatase; CS, company submission; mCPRC, metastatic castration-resistant prostate cancer; NE, not estimable; NR, not reported; PFS, progression free survival; PSA, prostate-specific antigen"	The company requests that the text is updated to: "Key: ALP, alkaline phosphatase; CS, company submission; mCPRC, metastatic castration-resistant prostate cancer; NE, not estimable; NR, not reported; PFS, progression free survival; PSA, prostate-specific antigen; **SmPC, Summary of Product Characteristics**"	Typographical error (missing abbreviation)	Corrected.
Section 4.2.6.3, Page 104, Table 32	The company requests that the text is updated to: "Key: MAIC, matched adjusted indirect comparison"	Typographical error (missing abbreviation)	Corrected.
Section 4.2.7.1, Page 105 "The palliative care utility used was again taken from TA377 which used Sandblom et al (utility: 0.5)."	The company requests that the text is updated to: "The palliative care utility used was again taken from TA377 which used Sandblom **2004[x]** (utility: 0.5)."	Typographical error (reference missing from document)	Corrected.
Section 4.2.7.1, Page 107 "When compared to the data used in TA951[62] (which came from **PROpel**) the values used in the companies' model were considerably lower."	The company requests that the text is updated to: "When compared to the data used in TA951[62] (which came from **PROpel**) the values used in the **company's** model were considerably lower."	Typographical error	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.8.1, Page 110 "The EAG also noted that enzalutamide the primary patent for enzalutamide in the UK is set to expire in 2026."	The company requests that the text is updated to: "The EAG also noted that ~~**enzalutamide**~~ the primary patent for enzalutamide in the UK is set to expire in 2026."	Typographical error (delete repeated word)	Corrected.
Section 4.2.8.2, Page 111 **"**Wastage was included in the model for IV drugs using method of moments with weight data based on weight data based on Pfizer data on file (2022), which reported a mean weight of 82.54 kg and mean BSA of 1.99 m² for patients in Cohort 1 of **TALAPRO-2**."	The company requests that the text is updated to: "Wastage was included in the model for IV drugs using method of moments with weight data ~~**based on weight data**~~ based on Pfizer data on file (2022), which reported a mean weight of 82.54 kg and mean BSA of 1.99 m² for patients in Cohort 1 of **TALAPRO-2**."	Typographical error (delete repeated wording)	Corrected.
Section 6.2.3, Page 125: "The EAG base case in the comparison to olaparib with abiraterone excluded skeletal related events as the EAG did not consider the companies method for inclusion of SREs in the model to be robust."	The company requests that the text is updated to: "The EAG base case in the comparison to olaparib with abiraterone excluded skeletal related events as the EAG did not consider the **company's** method for inclusion of SREs in the model to be robust."	Typographical error.	Corrected.
Section 6.3.2, Page 129: "The cost difference between olaparib with abiraterone and talazoparib and enzalutamide increased marginally from [redacted] in the corrected company base case to [redacted] in the EAG deterministic base	The company requests that the text is updated to: "The cost difference between **enzalutamide monotherapy** and talazoparib **with** enzalutamide increased marginally from [redacted] in the corrected company base case to [redacted]	Typographical error.	Corrected.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
case (confidential discounts only included for talazoparib; **Error! Reference source not found.**)."	in the EAG deterministic base case (confidential discounts only included for talazoparib; **Error! Reference source not found.**)."		

Confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 1.4, Page 17 "The ICER for the comparison to enzalutamide (not including discounts other than talazoparib) was higher than in the comparison to olaparib with abiraterone (vs in the EAG base case)."	The direction of the ICER should be underlined and highlighted blue to represent data CIC data.	Underline and highlight blue the phrase " "	Edited in-line with company's suggestion.
Section 3.2.3.4, Page 54	The proportions of patients with dose reductions should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the values and .	Edited in-line with company's suggestion.
Section 3.2.3.4, Page 54-55	The main cause of dose reductions should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrases " " and " ".	Edited in-line with company's suggestion.
Section 3.2.3.4, Page 55	The proportion of patients experiencing serious treatment-emergent adverse events should be underlined and	Underline and highlight in blue the values " " and .	Edited in-line with company's suggestion.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	highlighted blue to represent CIC data.		
Section 3.3.2.1, Table 21, Page 65	The TALAPRO-2 median follow-up time should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the value "[redacted]"	Edited in-line with company's suggestion.
Section 3.4.1.1, Page 75	The talazoparib median time on treatment should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the value "[redacted]".	Edited in-line with company's suggestion.
Section 4.2.6.1, Page 87	The outcomes of the MAIC and modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the values [redacted], and [redacted].	Edited in-line with company's suggestion.
Section 4.2.6.1, Page 87	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent data CIC data.	Underline and highlight in blue the phrases "[redacted]", "[redacted]", "[redacted]"	Edited in-line with company's suggestion.
Section 4.2.6.1, Page 88	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrases "[redacted]", "[redacted]", "[redacted]", "[redacted]"	Edited in-line with company's suggestion.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 4.2.6.1, Page 88	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrase "[redacted]"	Edited in-line with company's suggestion.
Section 4.2.6.1, Page 90	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrase "[redacted]"	Edited in-line with company's suggestion.
Section 4.2.6.2, Page 93	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrases "[redacted]", "[redacted]", "[redacted]"	Edited in-line with company's suggestion.
Section 4.2.6.2, Page 94	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrases "[redacted]", "[redacted]"	Edited in-line with company's suggestion.
Section 4.2.6.3, Page 99	The outcomes of the modelled parametric curves should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrase "[redacted]", "[redacted]", "[redacted]", "[redacted]"	Edited in-line with company's suggestion.
Section 4.2.7.1, Page 109	The outcomes from unpublished trial data should be underlined and highlighted blue to represent CIC data.	Underline and highlight in blue the phrase "[redacted]"	Edited in-line with company's suggestion.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 5.2.1, Page 116	The outcomes of the deterministic sensitivity analyses should be underlined and highlighted blue to represent CIC.	Underline and highlight in blue the phrases "[redacted]", "[redacted]", "[redacted]", "[redacted]".	Edited in-line with company's suggestion.
Section 5.2.3, Page 118	The outcomes of the scenario analyses should be underlined and highlighted blue to represent CIC.	Underline and highlight in blue the phrases "[redacted]", "[redacted]", "[redacted]", "[redacted]"	Edited in-line with company's suggestion.

References

1. George DJ, Ramaswamy K, Yang H, et al. Real-world overall survival with abiraterone acetate versus enzalutamide in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis*. Dec 2024;27(4):756-764. doi:10.1038/s41391-024-00816-0
2. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM evidence*. 2022;1(9):EVIDoa2200043.
3. Agarwal N, Azad AA, Carles J. Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2023 2023;402:291-303.
4. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. May 10 2013;31(14):1748-57. doi:10.1200/jco.2012.43.1882
5. Lee AM, Saidian A, Shaya J, et al. The Prognostic Significance of Homologous Recombination Repair Pathway Alterations in Metastatic Hormone Sensitive Prostate Cancer. *Clin Genitourin Cancer*. Dec 2022;20(6):515-523. doi:10.1016/j.clgc.2022.06.016