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

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

Contents:

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 18 September 2025. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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1	***Proposed optimised recommendation versus enzalutamide*** Pfizer proposes talazoparib with enzalutamide (TALA+ENZA) for an optimised recommendation in adult patients with untreated hormone relapsed metastatic prostate cancer (mCRPC) when chemotherapy is not clinically indicated, only if, • Abiraterone or abiraterone based treatments are unsuitable or not tolerated. The above proposal is based on the following rationale: • Based on feedback from clinical and patient experts during this submission, there is a distinct population of patients with mCRPC who are currently ineligible for a poly-ADP-ribose polymerase inhibitor (PARPi) and androgen receptor pathway inhibitor (ARPi) combination due to co-morbidities that may preclude the use of abiraterone (ABI) based therapy (which also involves concomitant corticosteroid administration with prednisolone). Therefore, in the current treatment landscape for patients with mCRPC, there is a significant unmet need for an alternative first-line PARPi and ARPi combination that does not include ABI or a corticosteroid. • Clinical experts noted that patients with cardiovascular disease including, but not limited to, hypertension, angina or previous myocardial infarction may not be suitable for ABI. This is due to the potential risks of hypertension, hypokalaemia and fluid retention compromising their underlying medical conditions.[1] • TALA+ENZA also provides a steroid-free option compared with treatments that include ABI, which requires concomitant prednisolone. Therefore, TALA+ENZA could be an option for patients who cannot use steroids long-term, such as those with diabetes or osteoporosis. • To further explore the patient population where ABI or ABI based treatments would not be a preferred choice, Pfizer conducted a targeted desktop search for published real-world evidence (RWE) to identify the

	prevalence of cardiovascular conditions and diabetes in treatment naïve patients with mCRPC. A RWE study by Chowdhury et al.[2], which utilised patient record data from treatment naïve males with mCRPC in the multicentre Prostate Cancer Registry (which includes UK amongst other 15 European countries) was identified. Study findings estimated that 65.2% of treatment naïve males with mCRPC had cardiovascular conditions and 16.4% had diabetes.[2] As highlighted by clinical experts, these patients may be unsuitable for ABI based therapy, and therefore ENZA or TALA+ENZA may be preferred.

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2	***Addressing Existing Uncertainty*** As enzalutamide is the only relevant comparator for the proposed optimised population, all but one of the uncertainties sighted by the committee to adopt the lower end of the cost-effectiveness threshold, have been addressed: • ***None of the indirect treatment comparison approaches were deemed suitable***: the comparison between TALA+ENZA and ENZA is more robust, supported by the TALAPRO-2 randomised controlled trial, which provides head-to-head evidence and removes uncertainties from indirect treatment comparisons and population adjustment methods. • ***All comparators have not been modelled in the same population and a fully incremental analysis was not provided:*** a fully incremental analysis is no longer relevant given there is only one relevant comparator within the proposed optimised recommendation. However, Pfizer has also provided a full incremental analysis in Section 3 below. The analysis includes all comparators (TALA+ENZA, ENZA, OLA+ABI and ABI), where OS and rPFS for TALA+ENZA and ENZA are based on unweighted patient-level data from TALAPRO-2. This has been provided to aid committee decision making despite ENZA being identified as the only relevant comparator in the proposed optimised population. • ***Inconsistent modelling of time on treatment across the treatment arms***: this is no longer relevant for the optimised recommendation given that for the TALA+ENZA and ENZA treatment arms, patient-level data from TALAPRO-2 was used to inform TTD, as was therefore consistent across arms. In the draft guidance document, the committee agreed it was appropriate to assume that TTD is equal to rPFS for each treatment. In the fully incremental analysis provided in Section 3 below, the committee preferred assumption of TTD=rPFS is applied in the OLA+ABI treatment arms due to lack of available TTD data. In the ABI treatment arm TTD was assumed identical to the ENZA arm for simplicity (as per the EAG preferred base case). • ***Post-progression utility values were not considered generalisable to NHS practice****:* Pfizer agrees with the EAG and committee's preferred approach for including a single utility value for the full post-progression health state. However, the EAG's preferred post-progression utility of 0.775 is towards the higher end of the plausible range based on

	available evidence and may bias against TALA+ENZA. Therefore, to better reflect NHS practice, Pfizer applied a single post-progression utility value of 0.70. This value represents a more plausible base case which is the midpoint of the plausible range identified in the literature mentioned in the draft guidance (0.65-0.775). Scenarios investigating other plausible post-progression utilities within the range identified from the literature, specifically 0.65 and 0.75, are also presented in Section 5 of the response. Considering all key uncertainties associated with decision-making are no longer relevant with the optimised recommendation or are addressed in scenario analyses, the NICE committee should consider an acceptable ICER towards the higher end of the range NICE considers a cost-effective use of NHS resources.

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3	***NICE committee request for a full incremental analysis including all comparators*** Given ENZA is the only appropriate comparator, for the proposed optimised population, the cost-effectiveness model including TALA+ENZA and ENZA Pfizer shared with NICE in response to the evidence assessment group (EAG) clarification question B2 ("ID4004_Prostate talazoparib clarification question B2_Enza CEM_15MAY25_CON.xlsb") and the model with revisions by EAG including EAG's preferred base case Copy of ID4004 OLA+ABI EAG base case PAS.PSA.CON fixed 4-8 050825sk are the appropriate models for the decision making. Nonetheless, as requested in the Draft Guidance document[3], to aid committee decision making, Pfizer have provided a full incremental analysis including TALA+ENZA, ENZA, OLA+ABI and ABI, where OS and rPFS for TALA+ENZA and ENZA are based on unweighted patient-level data from TALAPRO-2.Pfizer acknowledge this is not a perfect solution and this is why a fully incremental analysis was not previously provided. However, as ENZA is the only relevant comparator for the population of interest, where ABI or ABI based treatments are unsuitable or not tolerated, it is not necessary to interpret and use comparisons beyond the head-to-head comparison of TALA+ENZA against ENZA in the full incremental analysis for decision making. The latest cost-effectiveness model comparison of TALA+ENZA against OLA+ABI with revisions by EAG including EAG's preferred base case ("Copy of ID4004 OLA+ABI EAG base case PAS.PSA.CON fixed 4-8 050825sk.xlsb") was used as the basis for developing the full incremental analysis. The base case inputs and settings for the full incremental analysis were aligned with EAG's preferred base casein the model comparing TALA+ENZA against ENZA (e.g. the use of unweighted OS and rPFS data and parametric curves for TALA+ENZA and ENZA, base case OS and rPFS extrapolations), with exception to the utility values used post-progression, to make sure the full incremental analysis have mostly similar results versus the previous EAG revised model comparing TALA+ENZA against ENZA.

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	For the indirect comparison to OLA+ABI, hazard ratios (HRs) for OLA+ABI against TALA+ENZA based on the fixed effects model of the proportional hazards network meta-analysis (NMA) using latest data cutoff of TALAPRO-2 (cutoff date 3rd September 2024) was used in the base case for modelling rPFS and OS for OLA+ABI. OS and rPFS HRs based on the random effects model and rPFS time-varying HRs based on fractional polynomial (FP) NMA were included as scenarios. The weighted matching-adjusted indirect comparison (MAIC) method to compare TALA+ENZA against OLA+ABI for OS and rPFS which was used in the original Pfizer submitted model is also available in the full incremental analysis; however, this option is only valid for comparing TALA+ENZA against OLA+ABI as weighted OS and rPFS TALAPRO-2 data were used. EAG preferred base case settings related to the OLA+ABI comparison were used in the full incremental analysis base case with the exception that the NICE committee's preferred assumption of assuming TTD the same as rPFS for OLA+ABI was used as the base case for the full incremental analysis, because the assumption was deemed most appropriate for modelling TTD for OLA+ABI. Also, a post-progression value of 0.70 was used instead of the 0.775 in the EAG's preferred base case; 0.775 is towards the higher end of the plausible range based on available evidence and may bias against TALA+ENZA, whereas, 0.70 is a more plausible base case which is in the middle of the plausible range identified in the literature and stated in the draft guidance (0.65-0.775). For the indirect comparison to ABI, as suggested in the Draft Guidance document[3], it was assumed ABI is identical to ENZA in the model (OS, rPFS, TTD, safety, subsequent treatments, etc.) apart from first line drug acquisition costs. Therefore, ABI and ENZA have the same life years and quality-adjusted life years (QALYs) results in the full incremental analysis. Note, assuming ABI and ENZA are clinically equivalent does not align with the NMA presented during the initial stages of this STA, however, this has been done here for simplicity and to align with EAG's preferred assumptions.

Please refer to response 4 to NICE's request for additional indirect treatment comparison for the rationale for not providing additional indirect treatment comparisons.

A summary of key base case settings used in the full incremental analysis is presented in Table 1.

Table 1: Summary of key base case settings used in the full incremental analysis

	Base case setting	**Justification (if not same as EAG's preferred base case)**
TALAPRO-2 unweighted OS and rPFS data and extrapolations	Unweighted	N/A
TALA+ENZA and ENZA rPFS extrapolations	Gamma	N/A
TALA+ENZA and ENZ OS extrapolations	Generalized gamma	N/A
TALA+ENZA TTD – TALA	Log-logistic	N/A
TALA+ENZA TTD – ENZ	Log-logsitic	N/A
ENZA	Log-logistic	N/A
OLA+ABI OS and rPFS	Proportional hazard NMA fixed effects hazard ratios applied to TALA+ENZA curves	Most suitable source of comparative efficacy for OLA+ABI
OLA+ABI TTD	Assumed equal to rPFS	Most suitable assumption of TTD for OLA+ABI
ABI results	Assumed equal to ENZ apart from first-line drug acquisition cost	N/A

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Post-progression and palliative care utilities	0.70	EAG's preferred base case is towards the higher end of the plausible range based on available evidence and may bias against TALA+ENZA and 0.70 is a more plausible base case which is in the middle of the plausible range identified in the literature and stated in the draft guidance (0.65-0.775)
End of life costs	Set to 0	N/A
Monitoring frequency	Same for all regimens	N/A
Drug wastage	Fully applied	N/A
Key: ABI, abiraterone; ENZA, enzalutamide; OLA, olaparib; OS, overall survival; PFS, progression-free survival; TALA, talazoparib; TTD, time to treatment discontinuation.		

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Results of the full incremental analysis

All results include confidential discount for TALA and no discounts for other drugs.

Deterministic results

Table 2 Deterministic pairwise comparison (TALA+ENZA vs. comparators) - including confidential discount for talazoparib

Treatment arm	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER / dominance
TALA+ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLA+ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; ICER, incremental cost effectiveness ratio; LYG, life years gained; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib; TTD, time to treatment discontinuation.

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Table 3 Deterministic fully incremental results - including confidential discount for talazoparib

Treatment arm	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER / dominance
ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; ICER, incremental cost effectiveness ratio; LYG, life years gained; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib; TTD, time to treatment discontinuation.

Probabilistic sensitivity analysis

Table 4 Probabilistic pairwise comparison (TALA+ENZA vs. comparators) - including confidential discount for talazoparib

Treatment arm	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER / dominance
TALA+ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLA+ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; ICER, incremental cost effectiveness ratio; LYG, life years gained; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib; TTD, time to treatment discontinuation.

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Table 5 Probabilistic fully incremental results - including confidential discount for talazoparib

Treatment arm	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER / dominance
ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TALA + ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLA + ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; ICER, incremental cost effectiveness ratio; LYG, life years gained; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib; TTD, time to treatment discontinuation.

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Figure 1: Cost-effectiveness plane, incremental total discounted costs and incremental discounted QALYs (TALA+ENZA vs comparators)

Key: ABI, abiraterone; ENZA, enzalutamide; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib.

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Figure 2: Cost-effectiveness acceptability curve

Key: ABI, abiraterone; ENZA, enzalutamide; OLA, olaparib; TALA, talazoparib.

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One-way sensitivity analysis

Figure 3: Tornado diagram, TALA+ENZA vs. ENZA

Key: AE, adverse events; ENZA, enzalutamide; rPFS, radiographic progression-free survival; SRE, skeletal related events; TALA, talazoparib.

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4	***Appropriateness of providing additional indirect treatment comparisons*** As discussed above, TALA+ENZA should be recommended for patients where abiraterone or abiraterone based treatments are unsuitable or not tolerated. This means that ENZA is the only appropriate comparator for TALA+ENZA. TALAPRO-2 provides head-to-head evidence comparing TALA+ENZA against ENZA. Nonetheless, for completeness, we have provided context below for committee, explaining why further indirect comparisons are not deemed necessary. The head-to-head randomised evidence based on the TALAPRO-2 randomised controlled trial is considered the most robust comparative evidence possible for the relevant comparator. The head-to-head comparison maintains randomisation and does not rely on indirect treatment comparisons and population adjustment methods. The use of the head-to-head comparison from TALAPRO-2 alone will lead to reduced uncertainty in the cost-effectiveness analysis for TALA+ENZA against ENZA. The proportional hazards (PH) assumption was assessed within TALAPRO-2 for OS and rPFS. The log-cumulative hazard curves for OS were approximately parallel throughout follow-up, suggesting the PH assumption was reasonable (Figure 4); some overlap during the start of follow-up was acceptable. Additionally, the curve on the Schoenfeld residuals formed an approximate straight line, supporting proportionality (Figure 5). Furthermore, the statistical test was not significant, which suggested that the PH assumption was not violated (Schoenfeld, P = 0.8358). Overall, findings suggested the PH assumption was reasonable for OS. The hazard plot for OS (Figure 6) demonstrated that the smoothed hazard over time for both treatments have a similar distributional shape.

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Figure 4: Log-cumulative Hazard Plot for Overall Survival, All-Comers Population (Cohort 1)

Figure 5: Schoenfeld Residuals Plot and Test for Overall Survival, All-Comers Population (Cohort 1)

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Figure 6: Hazard Plot for Overall Survival, All-Comers Population (Cohort 1)

The log-cumulative hazard curves for rPFS were only crossing at a very early time but did not cross at later times (Figure 7). The crossing in the curves was relatively minor and only occurred early in the trial period, and the curves were then approximately parallel from approximately 10 months. However, the curve on the Schoenfeld residual plot showed some evidence of non-PH during the initial follow-up period (Figure 8) and the Schoenfeld residual test value of 0.0238 provided evidence against the PH assumption. A significant value of this test indicates that there is evidence of time-varying effects, which does not support the assumption of PH. Overall, there were some concerns of the PH assumption holding for rPFS. The hazard plot for rPFS (Figure 9) demonstrated that the smoothed hazard over time for both treatments have a similar distributional shape.

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Figure 7: Log-Cumulative Hazard Plot: Radiographic Progression-Free Survival, All-Comers Population (Cohort 1)

Figure 8: Schoenfeld Residuals Plot and Test for Radiographic Progression-Free Survival, All-Comers Population (Cohort 1)

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Figure 9: Hazard Plot for Radiographic Progression-Free Survival, All-Comers Population (Cohort 1)

The Draft Guidance document[3] suggested considering alternative approaches to indirect treatment comparisons that allow all comparators to be included within one analysis, preserve randomisation and can model flexible hazards over time. The committee specifically suggest the use of multilevel network meta-regression (ML-NMR) to determine the relative effect of each treatment option[4]. In response to the EAG questions, the results of Fractional polynomial (FP) NMA were presented. FP NMA meets the requirements for indirect treatment comparisons that allow all comparators to be included within one analysis, preserve randomisation and can model flexible hazards over time.

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 cost-effectiveness model. 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 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 cost-effectiveness model. 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 deviance information criterion.

No FP model was deemed suitable for OS and only three out of 35 tested first- and second-order FP models had appropriate convergence for rPFS due to the high quantity and quality of evidence required to estimate several complex parameters. Since more parameters must be estimated for ML-NMR than those needed for the FP NMA, ML-NMR methods are unlikely to converge similarly to FP NMA.

The implementation of ML-NMR is inappropriate for two reasons:

1. **ENZA is the only comparator treatment for comparing against TALA+ENZA in the proposed restricted population and TALAPRO-2 provides head-to-head comparison and best evidence for comparative efficacy for the two regimens**

2. **ML-NMR are unlikely to converge and provide valid relative efficacy results**

Table 6 describes the impact of applying alternative methods (PH NMA, MAIC and FP NMA) to estimate the relative effects for rPFS, measure as the difference in mean rPFS between TALA+ENZA versus the comparators ENZA and OLA+ABI. There is little difference between the indirect treatment comparison methods.

The difference between TALA+ENZA and ENZA is smallest when the PH NMA is used and is greatest when the FP NMA is used. The difference between TALA+ENZA and OLA+ABI is smallest when the MAIC is used and is greatest when the PH NMA is used.

No further indirect comparisons are deemed necessary to be implemented and incorporated into the cost-effectiveness model because:

- The PH NMA, MAIC and FP NMA are already implemented in the cost-effectiveness model and provide consistent results, and
- Other indirect treatment comparisons which preserve randomisation and can model flexible hazards over time are unlikely to converge and provide valid relative efficacy results

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Table 6: Difference in mean rPFS for each indirect treatment comparison conducted

Indirect treatment comparison model	TALA + ENZA vs	Difference in mean rPFS (months)
Proportional hazards NMA	ENZA	[redacted]
	OLA + ABI	[redacted]
MAIC	ENZA	[redacted]
	OLA + ABI	[redacted]
Fractional polynomial NMA	ENZA	[redacted]
	OLA + ABI	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; MAIC, matching adjusted indirect treatment comparison; NMA, network meta-analyses; OLA, olapraib; rPFS, radiographic progression-free survival; TALA, talazoparib.

5	**Scenario analysis on post-progression utility** The Draft Guidance document[3] notes that utility values for the post-progression disease state range from 0.65 to 0.775, as reported in NICE TA951 and a recent literature review[5]. The committee stated that a different utility value could be considered for the post-progression health state instead of the 0.775 value that was used in the EAG's preferred base case. As mentioned above, the EAG's preferred base case is towards the higher end of the plausible range based on available evidence and may bias against TALA+ENZA. Therefore, using a value of 0.70 is a more plausible base case which is in the middle of the plausible range identified in the literature and stated in the draft guidance (0.65-0.775). Two alternative scenarios were also explored with post-progression (including palliative care) utilities being 0.65 and 0.75. The deterministic pairwise results are presented in Table 7 and Table 8 which show that the incremental cost-effectiveness ratios for TALA+ENZA against comparators all improved (lower) versus the EAG's preferred base case. Pfizer believe that the EAG's preferred base case for post-progression utility is towards the higher end of the plausible range based on available evidence and may bias against TALA+ENZA and a more plausible base case, e.g. post-progression utility of 0.70, should be considered.

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Table 7 Deterministic pairwise comparison (TALA+ENZA vs. comparators) - including confidential discount for talazoparib and post-progression (and palliative care) utility = 0.65

Treatment arm	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER / dominance
TALA+ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLA+ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; ICER, incremental cost effectiveness ratio; LYG, life years gained; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib; TTD, time to treatment discontinuation.

Table 8 Deterministic pairwise comparison (TALA+ENZA vs. comparators) - including confidential discount for talazoparib and post-progression (and palliative care) utility = 0.75

Treatment arm	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER / dominance
TALA+ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OLA+ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ENZA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ABI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABI, abiraterone; ENZA, enzalutamide; ICER, incremental cost effectiveness ratio; LYG, life years gained; OLA, olaparib; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life years; TALA, talazoparib; TTD, time to treatment discontinuation.

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

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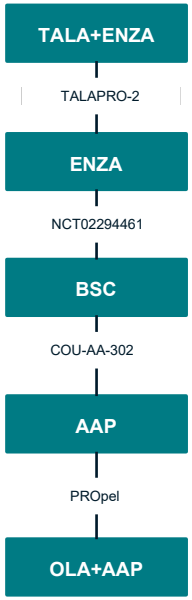
Appendix

Proportional hazards assessment for studies including abiraterone

In the submission, Pfizer presented indirect treatment comparisons for rPFS and OS based on the network presented in Figure 10

Figure 10: Network of evidence including abiraterone-containing regimens for rPFS and OS



While abiraterone-containing regimens are no longer relevant comparators for talazoparib plus enzalutamide, proportional hazards assessment figures for PROpel, COU-AA-302 and NCT02294461 are presented for completeness.

Table 9: Assessment of the proportional hazards assumption

Trial	Overall Survival	Progression-free Survival
COU-AA-302	No evidence against the proportional hazards assumption	Schoenfeld plot and test provides some evidence against the proportional hazards assumption
NCT02294461	No evidence against the proportional hazards assumption	Kaplan-Meier, log-cumulative hazard, Schoenfeld residual plot and test suggest that the proportional hazards assumption does not hold
PROpel	Schoenfeld test provides some evidence against the proportional hazards assumption, however the other diagnostics do not suggest this	No evidence against the proportional hazards assumption
Note: It was not possible to estimate smoothed hazards for COU-AA-302 OS and NCT02294461 PFS.		

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Figure 11: Kaplan-Meier, log-cumulative hazard, Schoenfeld residual and smoothed hazards plot for overall survival in COU-AA-302

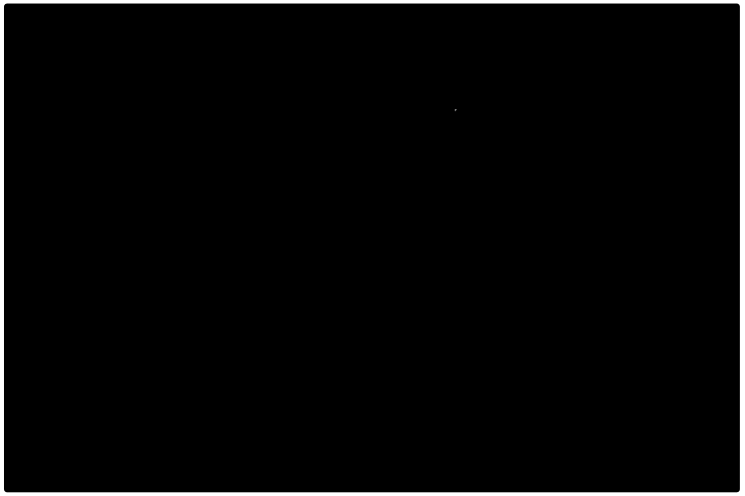

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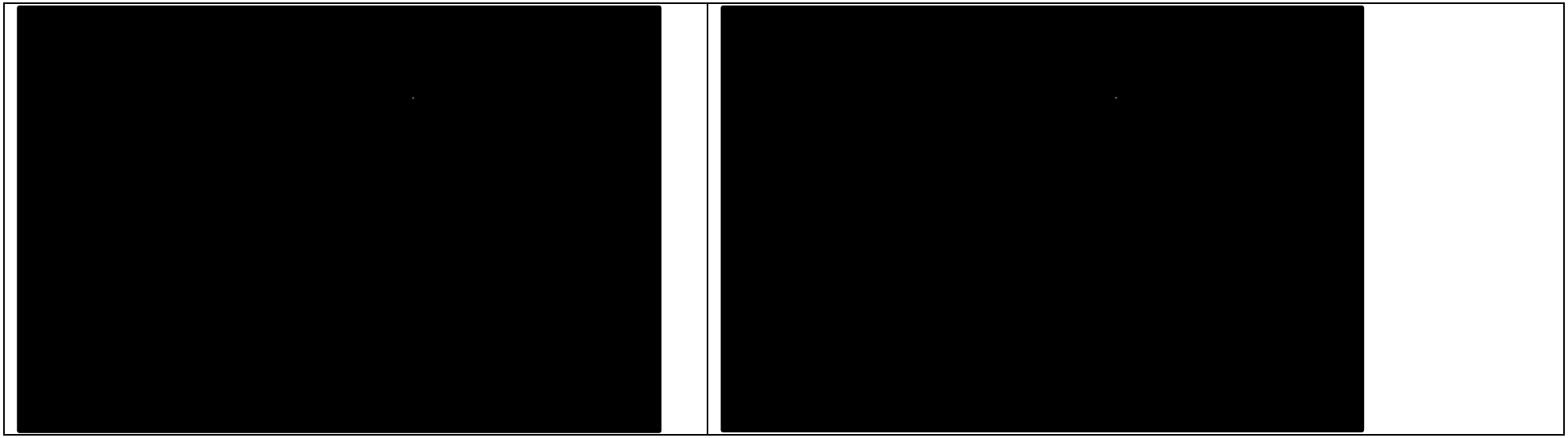
Figure 12: Kaplan-Meier, log-cumulative hazard, Schoenfeld residual and smoothed hazards plot for overall survival in NCT02294461



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

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[redacted]	[redacted]

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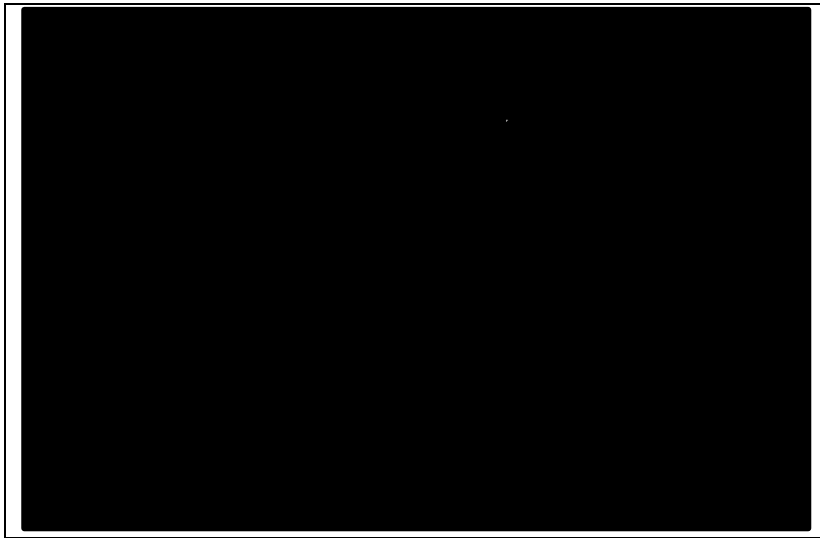
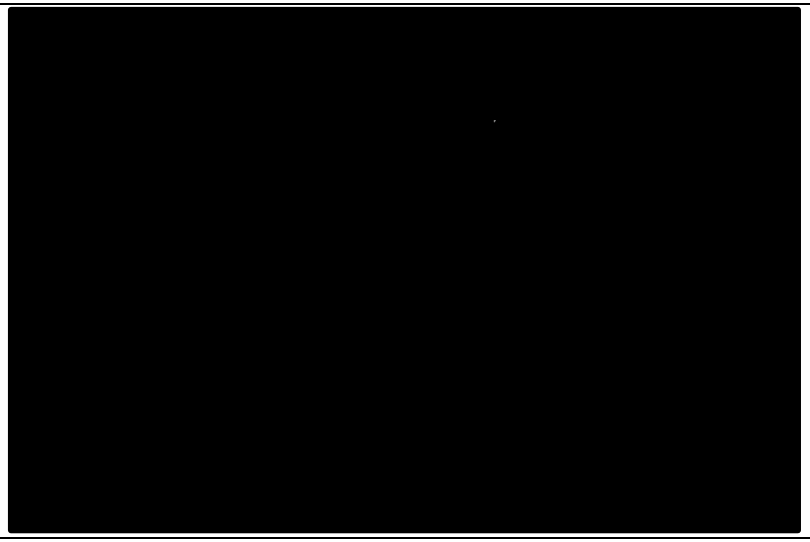
Figure 13: Kaplan-Meier, log-cumulative hazard, Schoenfeld residual and smoothed hazards plot for overall survival in PROpel





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

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[redacted]	[redacted]

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Figure 14: Kaplan-Meier, log-cumulative hazard, Schoenfeld residual and smoothed hazards plot for progression-free survival in COU-AA-302

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

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[redacted]	[redacted]

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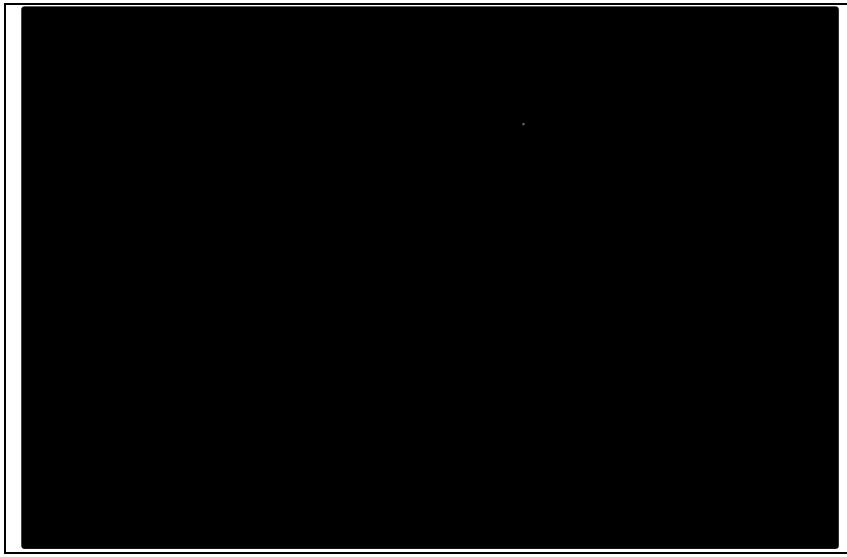
Figure 15: Kaplan-Meier, log-cumulative hazard, Schoenfeld residual and smoothed hazards plot for progression-free survival in NCT02294461



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

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[redacted]	[redacted]

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Figure 16: Kaplan-Meier, log-cumulative hazard, Schoenfeld residual and smoothed hazards plot for progression-free survival in PROpel

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

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[redacted]	[redacted]

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

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

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	In 2024, Prostate Cancer UK received £300 in funding from Pfizer as an unrestricted small donation. No other funding has been received from the submitting company or comparator treatment companies in the last 12 months.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We would urge the committee to reconsider this treatment due to the improvements in both

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

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	overall survival and radiographic progression-free survival it provides compared to enzalutamide alone, as shown through direct comparison in the TALAPRO-2 trial. However, we appreciate the committee's caution around the other comparison analyses considered during this appraisal.
2	We believe that the committee's report contains an accurate summary of the evidence and accept their conclusion that this treatment cannot at this time be recommended for the population being evaluated. However, we are concerned that this recommendation means that patients who have fewer options available to them will miss out on an effective treatment.
3	While enzalutamide, abiraterone plus prednisolone and the combination of Olaparib and abiraterone are all treatment options for the population being considered in this appraisal, in practice many patients are contraindicated to abiraterone. Therefore, we see the primary benefit of this treatment as being an alternative and more clinically effective option for those who would otherwise only have the option of enzalutamide monotherapy. There is substantial unmet need for this group of patients as they do not currently have an androgen receptor pathway inhibitor (ARPi) / alternative poly-ADP ribose polymerase inhibitor (PARPi) combination treatment available to them, as has been recognised by the committee. We therefore would urge the committee to consider this treatment specifically for patients who are contraindicated to abiraterone. Consideration of the treatment for this group would ensure that the patients we believe would benefit most don't miss out due to insufficient evidence and would address the committee's concerns about the indirect comparison analyses.
4	While we believe that awareness of the added benefits of this treatment for HRR-deficient patients is important for clinical decision making, we support the committee's decision to assess the treatment beyond this subgroup due to its broader benefits for overall survival and radiographic progression-free survival.
5	We would also urge the committee to consider that this treatment is approved for patients in Scotland, following its appraisal by the Scottish Medicines Consortium (SMC) earlier this year.
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. 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 submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

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

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	Omi Parikh
Organisation	N/A
Conflict	N/A
Comments on the DG:	

As a consultant oncologist who has been involved in treating prostate cancer for the last 18 years on behalf of the patients I was extremely disappointed to see the negative NICE recommendation for this combination treatment for this group of patients,

This is the only treatment for first line castrate resistant prostate cancer patients to have shown such a significant survival advantage.

This combination has shown a survival advantage of 8.8 months against active treatment.

The other treatment options which for first line mCRPC include:
docetaxel (2.4 months OS improvement against placebo),
abiraterone + prednosolone (4.4 months OS improvement against placebe),
enzalutamide (5 months OS improvement against placebo)
combi olaparib abiraterone and prednisolone (has shown a trend towards improved OS (7.4 months) but it was not statistically significant)
are significantly inferior to the statistically significant efficacy of talazoparib / enzalutamide combination.

I do feel that if there was breast cancer treatment that had nearly 4 month improvement in OS compared with all other previously proven treatments than it would have been NICE approved.

However, if due to cost constraints it is not possible to approve talazoparib enzalutamide combination for all patients it should still be considered for selected patients who are not eligible for the olaparib + abiraterone + prednisolone combination who would otherwise be getting enzalutamide alone.

Patients who have cardiac history or diabetes are generally preferentially prescribed enzalutamide rather than abiraterone and prednisolone and for these patients there is undoubtedly an unmet need and would benefit from having the option of talazoparib and enzalutamide.

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

A Single Technology Appraisal

EAG Review of Company's Response to Draft Guidance

Produced by	**Peninsula Technology Assessment Group (PenTAG)** **University of Exeter Medical School** **South Cloisters** **St Luke's Campus** **Heavitree Road** **Exeter** **EX1 2LU**
Authors	**Mr Ahmed Abdelsabour**, Research Associate[1] **Mr Alex Allen**, Research Fellow[1] **Ms Sophie Robinson**, Research Fellow[1] **Ms Charlotte R Kelman**, Research Assistant[1] **Dr Matthew Fittall**, **C**onsultant Clinical Oncologist[2] **Mr William Cross**, Consultant Urologist[3] **Prof G.J. Melendez-Torres**, Professor[1] **Prof Dawn Lee**, Associate Professor[1] [1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter [2] University College London Hospitals NHS Foundation Trust [3] Leeds Teaching Hospitals NHS Trust
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Declared competing interests of the authors

Rider on responsibility for document The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

1. INTRODUCTION

This document provides the Evidence Assessment Group's (EAG's) critique of the company's response to the draft guidance produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]. Each of the issues outlined in the company response are discussed in Section 2.

2. EAG REVIEW OF COMPANY COMMENTS

Comment 1: Proposed optimised recommendation versus enzalutamide

In the company's addendum they proposed an optimised recommendation in people who could be offered olaparib with abiraterone and prednisolone but not be offered abiraterone and prednisolone or enzalutamide monotherapy. However, the Committee agreed that there was no distinct population eligible for olaparib with abiraterone and prednisolone but not for the other comparators included in the scope.

In response to the draft guidance the company has proposed a different optimised recommendation in people who are eligible for talazoparib with enzalutamide and enzalutamide monotherapy but not eligible for olaparib with abiraterone and prednisolone or abiraterone and prednisolone. The key to this change is to be able to identify a population who are eligible for enzalutamide and PARP inhibitors but not eligible for abiraterone.

The EAG understands that people should not receive abiraterone if they are contraindicated for prednisolone, as prednisolone is required to prevent adrenal insufficiency and mitigate side effects. It also should not be received by people with severe liver impairment (Child-Pugh class C) or by people with hypersensitivity to abiraterone or its components[1]. The EAG's clinical experts agreed that people with any of those characteristics would not be offered abiraterone in their practices. However, they noted this is a small population.

The decision of whether to offer abiraterone to a person with cardiovascular disease (CVD) is less clear cut and focuses on caution and mitigation. They explained that CVD itself isn't an absolute contraindication to abiraterone, but the steroid requirement along with risks of hypertension, hypokalaemia, and fluid retention, make treating physicians cautious in people with recent myocardial infarction, decompensated/NYHA III–IV heart failure, uncontrolled hypertension, unstable angina, or significant arrhythmia. However, this is not all people with cardiovascular conditions as detailed by the company and people with poorly controlled CVD are relatively uncommon.

The company also sent an additional a Clinical Practice Research Datalink (CPRD) data analysis. The company interrogated the CPRD to find any person aged 18 or over with a record of prostate cancer from 2015 onwards. From this, they concluded there were [redacted] people with prostate cancer. They then looked at how many of that group had a cardiac or diabetes condition, but not a seizure record, and found that this equated to [redacted] of this group, [redacted]

people. It was not clear to the EAG what to conclude from this number. It represented all people with prostate cancer, not limited to people with mCRPC, it represented people at any line of treatment, not simply fist-line, and it took no account of previous treatments they may have received. Also, it took a broad definition of CVD, many of whom were eligible for abiraterone, and did not include people contraindicated for prednisolone, people with severe liver impairment, or people with hypersensitivity to abiraterone. Overall, the EAG did not consider it possible to draw any meaningful conclusions from the number presented.

A comment was also made by a consultant oncologist through the NICE website who observed that talazoparib with enzalutamide could still be considered for people who are not eligible for the olaparib with abiraterone and prednisolone. He elaborated that people who have a "cardiac history" or diabetes are generally preferentially prescribed enzalutamide rather than abiraterone and prednisolone. As noted above, the EAG's clinical experts agreed there are people with CVD who would not be offered abiraterone but this is not all people with CVD and is a smaller subgroup with poorly controlled CVD or recent myocardial infarction. They agreed with the consultant that, assuming no other limiting factors, abiraterone would be *less favoured* due to steroids in people with poorly controlled diabetes but stated that this can often be managed.

Comment 2: Addressing Existing Uncertainty

Addressing Existing Uncertainty

In Section 3.20 of the draft guidance, the committee stated their caution about recommending a technology because of a high level of uncertainty in the Incremental Cost-Effectiveness Ratio (ICER). This was specifically due to:

- inconsistent modelling of time on treatment across the treatment arms
- all comparators have not been modelled in the same population and a fully incremental analysis was not provided
- none of the indirect treatment comparison approaches were deemed suitable; specifically, the unanchored MAIC used in the base case was very uncertain
- the post-progression utility values in the company's base case were not considered generalisable to NHS practice and added further uncertainty to the model outcomes

The company address these four in their response and the EAG comment on their response below.

Inconsistent modelling of time on treatment across the treatment arms

For talazoparib with enzalutamide and enzalutamide (the relevant comparator for the optimised positioning), time to treatment discontinuation was informed by the unweighted TALAPRO-2 trial data, which the EAG considers broadly appropriate.

Comment 3: NICE committee request for a full incremental analysis including all comparators

The EAG agrees with the company that, given the revised positioning of talazoparib with enzalutamide and the updated population, the decision problem has changed, and olaparib with abiraterone and abiraterone monotherapy are no longer relevant comparators. As such, a fully incremental analysis was not required.

Comment 4: Appropriateness of providing additional indirect treatment comparisons

The company noted that their request for an optimised recommendation meant enzalutamide monotherapy was the only relevant comparator. We understand that the company used OS and rPFS curves fitted to TALAPRO-2 data for the model and this did not require an assumption of proportional hazards. Therefore, the EAG consider the concerns related to the proportional hazards assumption to have been addressed by the company.

The company go on to reply to the committee suggestion of the use of multilevel network meta-regression (ML-NMR) to address uncertainty linked to each of the three indirect treatment comparisons (ITCs) presented. The company noted, quite reasonably, that an ITC was not required for the optimised recommendation. The company also stated that the ML-NMR are unlikely to converge and provide valid relative efficacy results but the EAG was unable to confirm this within the timeframe of this critique to the consultation response.

Comment 5: Scenario analysis on post-progression utility

The EAG would like to clarify that it did not use a post-progression utility value 0.775 in the base case. Instead, the EAG applied a multiplier, which assumes a similar relative decrease from progression-free utility to that observed in the PROpel trial. This resulted in approximately a 5% decrease in utility, corresponding to an absolute decrease of [redacted].

The EAG agrees that the resulting post-progression utility estimate from PROpel lies towards the higher end of the plausible range, being relatively close to progression-free values. EQ-5D

responses from PROpel also suggested that quality of life was lower at 3 months post-progression compared with subsequent measures. This pattern may reflect patient stabilisation on subsequent treatments and improved symptom management, but it is also possible that sicker patients were less likely to complete questionnaires, particularly given the large number of PRO instruments administered.

The literature review by Castro et al.2025[3] reported a pooled post-progression utility estimate of 0.70 when limiting the analysis to clinical trials data. However, this meta-analysis did not include the October 2022 PROpel post-progression utility (0.775), which if incorporated, would have increased the pooled estimate.

Therefore, The EAG considers the company's suggestion of using 0.70 as the base case reasonable but notes a plausible range for post-progression utility could be between 0.70 and 0.775.

3. IMPACT ON COST-EFFECTIVENESS

In line with the Committee's preferred assumptions, the company excluded skeletal-related events, applied full drug wastage costs, and excluded end-of-life care costs (keeping only EAG corrected palliative care costs).

The company did not, however, assume time to discontinuation (TTD) equal to rPFS. Instead, TTD for talazoparib with enzalutamide and enzalutamide monotherapy was informed directly by TALAPRO-2 trial data. The EAG considers this approach reasonable, as the Committee's preference for TTD being equal to rPFS was primarily to address uncertainty around olaparib with abiraterone TTD, which is no longer a relevant comparator, still the EAG included a scenario where TTD=rPFS to test the potential impact of this assumption. This scenario is relevant if the Committee consider that patients would not discontinue treatment in line with the rules applied within the clinical trial. In TALAPRO-2, study treatment was discontinued in the following circumstances:

- Radiographic progression, unless the investigator considered the patient to still be deriving clinical benefit. Progression measured every 8 weeks until week 25 and every 12 weeks thereafter using RECIST. Continuation post-progression was allowed, until in the investigator's opinion the patient was no longer clinically benefitting.
- Occurrence of an AE leading to permanent discontinuation.
- Patient decision to discontinue treatment.
- Death.

The company applied a PPS utility of 0.70, which differs from the Committee's preferred value of 0.775. The EAG considers the company's assumption reasonable but also explored the impact of applying a plausible range (0.70, 0.75, and 0.775) in scenario analysis.

The results of the cost-effectiveness analysis, incorporating all relevant discounts, are presented in the cPAS appendix.

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