NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer

1 Recommendations

1.1 Talazoparib with enzalutamide can be used as an option for untreated hormone-relapsed metastatic prostate cancer in adults, only when:

- chemotherapy is not clinically indicated and
- abiraterone plus prednisolone is not tolerated, or
- there are clinical conditions that preclude the use of abiraterone plus prednisolone, and
- the company provides it according to the commercial arrangement (see section 2).

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

What this means in practice

Talazoparib with enzalutamide must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most

Issue date: January 2026

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suitable treatment option. Talazoparib with enzalutamide must be funded in England within 90 days of publication of this guidance.

There is enough evidence to show that talazoparib with enzalutamide provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

Usual treatment for untreated hormone-relapsed metastatic prostate cancer is abiraterone plus prednisolone, enzalutamide alone, or olaparib plus abiraterone and prednisolone.

For this evaluation, the company asked for talazoparib with enzalutamide to be considered only for people who cannot have abiraterone plus prednisolone. This does not include everyone who it is licensed for.

Clinical trial evidence shows that talazoparib plus enzalutamide increases how long people have before their condition gets worse and how long people live compared with placebo plus enzalutamide.

The cost-effectiveness estimates for talazoparib plus enzalutamide are within the range that NICE considers an acceptable use of NHS resources. So, it can be used.

2 Information about talazoparib

Marketing authorisation indication

2.1 Talazoparib (Talzenna, Pfizer) is indicated 'in combination with enzalutamide for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) in whom chemotherapy is not clinically indicated'.

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Dosage in the marketing authorisation

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

Price

2.3 The list price of talazoparib is £1,655 for a 30-pack of 0.10 mg or 0.25 mg capsules (excluding VAT; BNF online accessed January 2026).

2.4 The company has a commercial arrangement. This makes talazoparib available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Pfizer will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Hormone-relapsed metastatic prostate cancer (also known as metastatic castration-resistant prostate cancer) has spread beyond the prostate. The patient organisation submissions explained that for many it is a debilitating and life-changing condition. People may experience pain, anaemia, fatigue and bone damage. The patient expert explained that people have usually had several treatments before the metastatic stage. Some are still having side effects of previous treatments. The fear of living with the non-curative nature of this condition adds to a person's psychological burden

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and impacts their quality of life. The risk of prostate cancer increases with age. Prostate cancer is more common in people from Black African ethnic backgrounds, people with a family history of prostate cancer and people with a homologous recombination repair (HRR) mutation. People from an Ashkenazi Jewish ethnic background have a higher risk of having a breast cancer gene (BRCA) mutation and so a higher risk of prostate cancer.

Clinical management

Treatment options

3.2 First-line treatment options for hormone-relapsed metastatic prostate cancer when chemotherapy is not indicated include:

- olaparib plus abiraterone and prednisolone (from now, olaparib plus abiraterone) for people who cannot have or do not want chemotherapy (see NICE's technology appraisal guidance on olaparib with abiraterone for untreated hormone-relapsed metastatic prostate cancer [TA951])
- androgen receptor pathway inhibitor (ARPi) monotherapies, if neither have already been used:
  - abiraterone with prednisolone (from now, abiraterone; see NICE's technology appraisal guidance on abiraterone for treating hormone-relapsed metastatic prostate cancer before chemotherapy is indicated [TA387])
  - enzalutamide (see NICE's technology appraisal guidance on enzalutamide for treating hormone-relapsed metastatic prostate cancer before chemotherapy is indicated [TA377])
- 'watchful waiting'.

The patient expert submissions stated that there is a high unmet need for more first-line treatment options for hormone-relapsed metastatic prostate cancer. This is because of the non-curative nature of the

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cancer and to delay chemotherapy. They explained that, for people with the condition and their carers, ease of administration is a key factor in choosing a treatment. The patient expert noted that talazoparib plus enzalutamide provides a corticosteroid-free option compared with treatments that include abiraterone, which is always used with prednisolone (a type of corticosteroid). The clinical experts explained that, because abiraterone is associated with tolerability issues, an alternative poly-ADP ribose polymerase inhibitor (PARPi) and ARPi combination is needed. A clinical expert said that corticosteroid exposure should be taken into consideration because some people are unable to tolerate corticosteroids. The committee understood the unmet need in this population.

Population

3.3 The company's original submission positioned talazoparib plus enzalutamide as a treatment for:

- untreated hormone-relapsed metastatic prostate cancer when chemotherapy is not clinically indicated and
- when olaparib plus abiraterone would otherwise be offered.

The company proposed olaparib plus abiraterone as the main comparator for this population. At the first committee meeting the EAG, clinical experts and NHS Cancer Drugs Fund clinical lead could not identify a definable population for which abiraterone or enzalutamide monotherapy would not be an option, but olaparib plus abiraterone would be. The committee agreed that it was not feasible to make a recommendation for the subgroup the company had suggested and requested that the company provide evidence for the full population. In response to consultation, stakeholders stated it was also relevant to consider a population for which abiraterone or abiraterone-based treatments are unsuitable or not tolerated. The company presented a

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base case for this proposed optimised population of people who currently have enzalutamide monotherapy.

The committee considered how the proposed optimised population could be defined. The clinical lead for the Cancer Drugs Fund noted that Blueteq data from the last 6 months reported that about 58% of people had enzalutamide monotherapy, 28% had abiraterone (with prednisolone), and about 14% had abiraterone with olaparib (and prednisolone). The clinical experts stated that some people who would otherwise have enzalutamide monotherapy may want talazoparib plus enzalutamide, but they expect a higher proportion of people would continue to have enzalutamide monotherapy in clinical practice. The clinical experts explained that the decision for using abiraterone or enzalutamide is driven by a mix of clinical and patient factors. Abiraterone has an increased cardiovascular risk associated with it and monitoring is needed every few weeks in the first 3 to 4 months of starting treatment, including blood pressure and liver function tests. There is also pill burden and concerns about using corticosteroids. People with hormone-relapsed metastatic prostate cancer have already used hormone therapy before their cancer becomes hormone-relapsed, so adding corticosteroids on a long-term basis leads to concerns such as bone health. Clinical advice to the EAG was that there are absolute and relative contraindications to abiraterone. Absolute contraindications include when prednisolone is contraindicated, there is severe liver impairment (Child-Pugh class C) or there is hypersensitivity to abiraterone or its components. But this is a small population. Relative contraindications include cardiovascular disease and diabetes. For cardiovascular disease, there may be caution for some people with uncontrolled or risks of hypertension, hypokalaemia, fluid retention, recent myocardial infarction, decompensated NYHA-III-IV heart failure, unstable angina or significant arrhythmia. But most people's

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cardiovascular disease is relatively well controlled. For diabetes, this risk can be managed. But enzalutamide monotherapy may be preferred over abiraterone-based treatments to avoid corticosteroids in poorly controlled diabetes. A clinical expert explained that the decision on whether or not to offer abiraterone is nuanced. For example, in relation to cardiovascular disease, well-controlled hypertension is not an absolute contraindication to abiraterone. But also, a contraindication is not limited to only a recent myocardial infarction. There may be many more people with cardiovascular disease, osteopenia, osteoporosis, history of fractures, and liver dysfunction that there may be more caution in using abiraterone than enzalutamide. The clinical lead for the Cancer Drugs Fund noted there may be people who would choose abiraterone over enzalutamide. They advised that fatigue is a common side effect of enzalutamide, which also has challenging drug-drug interactions including with anti-hypertensives and statin drugs. They stated that limiting the population to people with absolute contraindications would be too narrow to address an unmet need in clinical practice. Also, people who cannot tolerate abiraterone or enzalutamide can switch to enzalutamide or abiraterone respectively within the first 3 months if their cancer has not progressed on the initial treatment. The committee agreed there is a population of people with untreated hormone-relapsed metastatic prostate cancer for whom chemotherapy is not yet clinically indicated. And there are clinical conditions that preclude the use of abiraterone, beyond its contraindications. It was not possible to define these conditions further because clinical judgement would be needed for an individual on the risks associated with these conditions. There would also be a population of people who cannot tolerate abiraterone and could switch to an enzalutamide-based treatment if their cancer had not progressed on abiraterone. The committee concluded it was appropriate to evaluate talazoparib plus enzalutamide for:

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- the whole population in which it is indicated. The comparators for this population are abiraterone, enzalutamide, and olaparib plus abiraterone
- an optimised population in which clinical conditions preclude the use of abiraterone, or it is not tolerated. The comparator for the optimised population is enzalutamide monotherapy.

Clinical effectiveness

TALAPRO-2

3.4 The clinical evidence for talazoparib plus enzalutamide came from TALAPRO-2, a randomised, double-blind, placebo controlled, phase 3 trial. The trial started enrolment with cohort 1 (805 people), an 'all-comers' population that included all participants irrespective of HRR mutation status. The trial compared talazoparib plus enzalutamide (402 people, 21% HRR deficient) with enzalutamide plus placebo (403 people, 21% HRR deficient) as first-line treatment of hormone-relapsed metastatic prostate cancer in adults in whom chemotherapy is not clinically indicated. The primary outcome was radiographic progression-free survival (rPFS) assessed by blinded independent central review. Secondary outcomes included overall survival (OS), adverse events, health-related quality of life, time to starting cytotoxic chemotherapy, time to starting subsequent antineoplastic treatment and time to first symptomatic skeletal-related event. After cohort 1 enrolment completion, only people with HRR mutations were recruited into cohort 2 of the trial. Cohort 2 included 399 people (200 people having talazoparib plus enzalutamide and 199 people having enzalutamide plus placebo).

TALAPRO-2 results

3.5 The company presented results from cohort 1 in its base case. Talazoparib plus enzalutamide showed a statistically significant improvement in OS compared with enzalutamide plus placebo (hazard ratio [HR] 0.796; 95% confidence interval [CI] 0.661 to 0.958; 2-sided

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p=0.0155). The median OS was 45.8 months (95% CI 39.4 to 50.8) in the talazoparib plus enzalutamide arm and 37.0 months (95% CI 34.1 to 40.4) in the enzalutamide plus placebo arm. For rPFS, talazoparib plus enzalutamide showed a statistically significant improvement compared with enzalutamide plus placebo (HR 0.667; 95% CI 0.551 to 0.807; 2-sided p<0.0001). The median rPFS was 33.1 months (95% CI 27.4 to 39.0) in the talazoparib plus enzalutamide arm and 19.5 months (95% CI 16.6 to 24.7) in the enzalutamide plus placebo arm. The committee concluded that talazoparib plus enzalutamide improved OS and rPFS compared with enzalutamide plus placebo.

HRR mutation subgroup

3.6 TALAPRO-2 prespecified subgroup analysis by HRR mutation. The EAG noted that this analysis was not provided in the company submission and was published in Agarwal et al. (2023). For rPFS, HRR status was a treatment effect modifier because the efficacy was reduced in HRR non-deficient or unknown tumours. For OS, talazoparib plus enzalutamide had a statistically significant benefit over enzalutamide plus placebo in HRR-deficient cancer, but the benefit was not statistically significant in HRR non-deficient or unknown tumours. At clarification, upon the EAG's request, the company provided TALAPRO-2 clinical efficacy results from cohort 2 (in which 100% had HRR-deficient tumours). The company noted that it was not seeking NICE recommendations for cohort 2 and the marketing authorisation was based on cohort 1 data. The EAG concluded that the treatment effect estimates for rPFS and OS were similar in the talazoparib plus enzalutamide arm for cohort 1 and cohort 2. The placebo plus enzalutamide arm outcomes were worse for cohort 2 compared with cohort 1. This suggested that enzalutamide did not work as well in cohort 2 compared with cohort 1. The EAG suggested that a separate subgroup analysis for the HRR-deficient population may be needed. The clinical experts explained that HRR deficiency is not part of national routine genetic testing in the NHS. There is lack of capacity with HRR

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testing and it is unlikely to be resolved soon. The committee understood that talazoparib plus enzalutamide was effective in the 'all-comers' group but showed additional benefit in the HRR-deficient group. It noted the HRR was not currently part of routine testing and this subgroup would be difficult to identify in the NHS. So, it concluded that the HRR-deficient subgroup did not need to be considered separately.

Indirect treatment comparisons

3.7 For evaluating the whole population, there were no clinical trials comparing talazoparib plus enzalutamide with olaparib plus abiraterone or abiraterone. So, the company did a network meta-analysis (NMA) to estimate the comparative efficacy of talazoparib plus enzalutamide against olaparib plus abiraterone for rPFS, OS and time to prostate-specific antigen progression. The network included 8 studies (TALAPRO-2, PROpel, BRCAAway, COU-AA-301 and COU-AA-302, NCT01591122, NCT02294461, Hu et al. 2020, PREVAIL) and 5 interventions (talazoparib plus enzalutamide, abiraterone, best supportive care, enzalutamide, olaparib plus abiraterone). The company used a Cox proportional hazards model within a Bayesian framework. The company used a random effects model in its base case. The results of the proportional hazards NMA are confidential and cannot be reported here. The EAG commented that there were no common comparators linking talazoparib plus enzalutamide with olaparib plus abiraterone in the network. As a result, the network was sparse and lacked direct evidence, with 4 pairwise comparisons across 5 studies connecting talazoparib plus enzalutamide with olaparib plus abiraterone. The EAG preferred the fixed effects model over the random effects model. This was because the network was a straight line, and the random effects estimate was only based on 1 comparator and 2 studies. Also, the fixed effects model was a better fit for both rPFS and OS outcomes. The EAG noted the assessment of the proportional hazards assumption in the PROpel trial from TA951, which compared olaparib plus abiraterone with abiraterone. It explained that the proportional hazards

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assumption was not met by the rPFS and OS input data from the studies in the NMA. This meant that results could be biased, leading to inaccurate conclusions. The EAG proposed that an unanchored matching-adjusted indirect comparison (MAIC) or fractional polynomials NMA might be more suitable.

The company presented an unanchored MAIC comparing talazoparib plus enzalutamide with olaparib plus abiraterone. The individual patient level data from TALAPRO-2 was matched with the PROpel olaparib plus abiraterone trial data. TALAPRO-2 data was reweighted to ensure that the underlying populations were similar. The company noted some differences between the trial populations but concluded that an unanchored MAIC was feasible. The EAG flagged that because of the differences in trial eligibility criteria, baseline pain scores were higher in PROpel than in TALAPRO-2 and it was not feasible to adjust for these. The EAG's clinical experts explained that pain is a prognostic factor and should be adjusted. The EAG concluded that the PROpel population's hormone-relapsed metastatic prostate cancer would be harder to treat and this favoured talazoparib and enzalutamide and caused uncertainty in the MAIC outcomes.

At clarification, the company provided a fractional polynomials NMA to accommodate non-proportional hazards and preserve randomisation. It was based on a network including 4 studies (TALAPRO-2, PROpel, NCT02294461 and COU-AA-302) and 5 interventions (talazoparib plus enzalutamide, abiraterone, best supportive care, enzalutamide, olaparib plus abiraterone). The OS analysis had convergence issues which meant a stable model fit was not identified and OS outcomes were not thought reliable. For rPFS, several plausible model fits were identified. Based on visual fit and low deviance information criterion, one model fit was considered best. The EAG considered the fractional polynomials NMA to

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be well conducted. It agreed that the OS outcomes from the fractional polynomials NMA were unreliable. The EAG questioned the extent of the validation done for the selection of the rPFS model fit.

The committee acknowledged the issues with the indirect evidence base leading to substantial uncertainty because:

- The MAIC:
  - was unanchored, despite a network being available
  - could not adjust for all prognostic factors
  - had uncertain outcomes
  - only included a pairwise comparison so excluded abiraterone and enzalutamide monotherapies.
- The proportional hazards NMA had non-proportionality in the network, although it did allow for all treatments to be included in the NMA and for randomisation to be preserved.
- The fractional polynomial NMA relaxed the proportional hazards assumption but did not converge for OS so did not provide usable outcomes.

  At the first meeting, the committee wanted to see further analysis using methods that preserve randomisation and can model flexible hazards over time to overcome the non-proportional hazards issue in the proportional hazards NMA. These approaches should allow for all comparators to be included within 1 analysis. The committee suggested considering alternative approaches (see NICE's Decision Support Unit technical support document 18 on methods for population-adjusted indirect comparisons) such as multilevel network meta-regressions. In response to consultation, the company stated that the committee's preference of exploring a multilevel network meta-regression was unlikely to provide valid relative efficacy results. This was because

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more parameters would need to be estimated than in the fractional polynomial NMA, so the data was also unlikely to converge (similar to the fractional polynomial NMA). The company provided a fully incremental analysis using the fixed effects model of the proportional hazards NMA to estimate the hazard ratios for olaparib plus abiraterone relative to talazoparib plus enzalutamide. This approach could give relative estimates of rPFS and OS for all comparators, but these would be uncertain. Enzalutamide and abiraterone were considered clinically equivalent in the fully incremental analysis (see section 3.9). The committee concluded that although the proportional hazards NMA provided estimates for the fully incremental analysis, all of the indirect treatment comparisons were highly uncertain.

Economic model

Company's modelling approach

3.8 The company used a 3-state partitioned survival model. The 3 health states were progression free, progressed disease and death. In the progressed disease health state, the cohort progresses onto palliative care after 1 line of subsequent treatment. The EAG explained that making this assumption meant that most of the time in the post-progression health state is spent in palliative care. This may not apply to a cohort having a fixed treatment duration and does not take account of multiple lines of subsequent treatment. The EAG did scenario analyses varying the time spent in palliative care and these made small differences to the incremental cost-effectiveness ratio (ICER). The committee acknowledged the palliative care modelling issue and noted the scenario analysis did not make a large difference to the outcomes. The committee concluded that the model structure was appropriate for decision making.

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Abiraterone and enzalutamide clinical equivalence

3.9 For evaluating the whole population, the company used data from TALAPRO-2 to model OS and rPFS in the talazoparib plus enzalutamide and the enzalutamide model arms. Hazard ratios derived from the proportional hazards NMA were applied to the talazoparib plus enzalutamide data to model OS and rPFS in the olaparib plus abiraterone model arm. At the first committee meeting, the EAG provided analyses that assumed abiraterone and enzalutamide were clinically equivalent in the economic model (HR for OS and rPFS, 1.00) and replaced enzalutamide monotherapy costs with abiraterone plus prednisolone costs. This approach was based on TA951, in which the committee concluded it was reasonable to assume clinical equivalence between abiraterone and enzalutamide to inform the economic modelling. The EAG also did scenario analyses applying alternative hazard ratios to OS and rPFS from both TA951 (OS HR of 1.19, 95% credible interval 1.10 to 1.30, which was also applied to rPFS) and the proportional hazards NMA from this evaluation (see section 3.7). These scenarios modelled the reduced clinical effectiveness of abiraterone compared with enzalutamide. All other inputs in the model, such as the adverse event rates, were the same for abiraterone and enzalutamide monotherapies. In response to consultation the company provided a fully incremental analysis using the same assumption as the EAG (that abiraterone and enzalutamide were clinically equivalent), rather than using data from the indirect treatment comparison. The committee noted the uncertainty of data informed by the indirect comparison. It concluded that the approach of assuming clinical equivalence of abiraterone and enzalutamide was suitable for decision making.

rPFS and OS extrapolations

3.10 In the company's economic model, independent parametric curves were fitted to the OS and rPFS data. The selections were based on visual and

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statistical fit, and external validation using TALAPRO-2 and TA951. In its original submission for both talazoparib plus enzalutamide and enzalutamide monotherapy treatment arms, the company fit:

- log-normal distributions to the OS curves
- log-normal distributions to the rPFS curves.

Log-normal was specifically chosen because it did not exhibit any kinks in the extrapolations. The EAG disagreed with the curve selections. It noted for OS, log-normal provided a poor statistical and visual fit. The EAG preferred the:

- generalised gamma distribution fit for OS
- gamma distribution for rPFS.

For rPFS, the EAG advised that the company's choice of log-normal is plausible when assessed independently of OS but noted that the rPFS and OS curves crossed. So, it preferred the gamma distribution for rPFS because it did not result in the curves crossing. During the committee meeting the company agreed with the EAG's preferred base case.

At the first committee meeting, the committee considered the available data and expert opinions. It concluded that for the comparison with enzalutamide monotherapy, the generalised gamma was the most appropriate parametric curve for extrapolating OS and the gamma distribution was the most appropriate for extrapolating rPFS. After consultation, the distributions used in the fully incremental analysis and the company's base case for the proposed optimised population (see section 3.3) were consistent with the committee's preferences for talazoparib plus enzalutamide and enzalutamide monotherapy agreed at the first committee meeting.

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Time on treatment assumptions

3.11 In the company's model, independent parametric curves were fitted to time to treatment discontinuation Kaplan–Meier data from TALAPRO-2. Log-logistic distribution was selected for talazoparib, enzalutamide (when used in combination) and enzalutamide monotherapy based on statistical and visual fit. The EAG agreed with the log-logistic distribution fitted for the talazoparib, enzalutamide (when used in combination) and enzalutamide monotherapy arms of the TALAPRO-2 Kaplan–Meier data. Time to treatment discontinuation data was not publicly available for olaparib plus abiraterone or for abiraterone. For olaparib plus abiraterone, the company assumed time to treatment discontinuation was the same as rPFS. The company said this was based on similar assumptions made in Canada's Drug Agency (CDA-AMC) submission for olaparib plus abiraterone. The EAG had concerns with the assumptions about time on treatment in the comparison with olaparib plus abiraterone. The EAG noted that the CDA-AMC submission assumed that time to treatment discontinuation was lower than rPFS. Since rPFS was shorter for olaparib plus abiraterone compared with talazoparib plus enzalutamide, the EAG would expect the same relationship for time to treatment discontinuation. So, using unadjusted data for the talazoparib plus enzalutamide treatment arm resulted in implausible outcomes. The results are marked confidential and cannot be reported here. The EAG's clinical experts noted that they would expect time to treatment discontinuation for each treatment to be similar to rPFS for that treatment. So, the EAG's preferred base case assumed that the observed relationship between time to treatment discontinuation and rPFS for talazoparib plus enzalutamide applied to olaparib plus abiraterone. To model time to treatment discontinuation with abiraterone, the relationship between time to treatment discontinuation and rPFS for enzalutamide was applied to abiraterone. The EAG did a scenario analysis in which time to treatment discontinuation was equal to rPFS across all treatment arms. The clinical experts explained that some

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people stop treatment because of toxicity. So, time to treatment discontinuation would be shorter than rPFS. But some people continue treatment after progression if they have no progression symptoms. The company confirmed that in TALAPRO-2 people could continue treatment beyond progression. The experts said that, on balance, they would expect the 2 outcomes to be similar. The committee said there was no strong justification to assume that time to treatment discontinuation and rPFS would be different for each individual treatment. The committee considered the evidence presented and that time to treatment discontinuation data was not available for all treatments. It concluded that assuming time to treatment discontinuation was equal to rPFS for each treatment was the most plausible assumption.

After consultation, the company's modelling in its base case for time to treatment discontinuation for talazoparib plus enzalutamide and enzalutamide monotherapy in people for whom abiraterone was unsuitable or not tolerated (its proposed optimised population) was informed by the unweighted TALAPRO-2 data. The EAG agreed this is appropriate because the preference for time to treatment discontinuation being equal to radiographic progression-free survival was mainly to address the uncertainty around olaparib plus abiraterone. The company agreed with the committee's preferences from the first committee meeting that for the full marketing authorisation population, time on treatment should equal radiographic progression-free survival for all treatments for consistency. The committee concluded that for the optimised population (see section 3.3) it is appropriate for time on treatment discontinuation to be informed by the TALAPRO-2 data, because this is the most relevant data from a head-to-head trial of talazoparib plus enzalutamide compared with enzalutamide plus placebo.

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Skeletal-related events

3.12 The costs and disutility associated with skeletal-related events per treatment arm were included by the company in its original base case that compared talazoparib plus enzalutamide with olaparib plus abiraterone. TALAPRO-2 data for skeletal-related events was used for talazoparib plus enzalutamide. For olaparib plus abiraterone, data was used from NICE's technology appraisal guidance on olaparib for previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer (pooled data from the ALSYMPCA, COU-AA-301 and AFFIRM trials) and TA951 (PROpel trial). Based on the trial event rates, the company assumed higher skeletal-related events for olaparib plus abiraterone compared with talazoparib plus enzalutamide. The EAG explained that the sources used for the olaparib plus abiraterone arm were 10 years old and that the patient population and bone health management has changed since then. It flagged that in TA951, treatment-specific differences in skeletal-related events were not assumed, and event rates were dependent on disease progression. The EAG's clinical experts agreed that most events are related to disease progression but some events, such as fractures, are related to androgen-deprivation treatment. They also did not agree with the higher event rates in the olaparib plus abiraterone arm. The EAG did not include skeletal-related events in its base case. The committee asked the clinical experts if they would expect to see a difference in skeletal-related events between treatment arms. The experts said they did not have experience with talazoparib plus enzalutamide and would have to rely on the TALAPRO-2 data. They noted that bone metastases and spinal cord compression are associated with the highest event rates for olaparib plus abiraterone and are related to disease progression. They noted that skeletal-related events have a substantial cost and quality-of-life burden. The committee understood that most skeletal-related events are related to disease progression. It was concerned that the company's analysis was a naive comparison associated with substantial uncertainty

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and that no attempt was made to link skeletal-related events to rPFS. It noted that excluding these from the base case did not make a big difference to the cost-effectiveness results. It concluded that, in the absence of a more robust comparison, it was satisfied with the EAG's assumption of excluding skeletal-related events from the base case. It decided to consider these as a potential uncaptured benefit related to improvements in disease control.

Utility values

3.13 The company used EQ-5D-5L data from TALAPRO-2 and mapped this to ED-5D-3L to inform the utility value in the progression-free health state, using the same value for all treatment arms. The utility value is confidential and cannot be reported here. TALAPRO-2 health-related quality of life data could not be used for the progressed health state because of the small sample size and missing data. So, the company used separate utility values for time in the post-progression and palliative care health states from TA377:

- post-progression (0.658), first-line post-progression weighted mean utility from Wolff et al. (2012) and Diels et al. (2015)
- palliative care (0.5), quality of life data from a Swedish prostate cancer cohort (Sandblom et al. 2004).

The EAG noted that most of the time in the progressed health state was spent with the palliative care utility (see section 3.8). It also noted that higher post-progression utility values ranging between 0.65 and 0.775 have been reported in TA951 and a recent literature review (Castro et al. 2025). The sources used by the company are 10 to 20 years old, so do not account for the treatment options available in the NHS today and do not reflect NICE's reference case. In the absence of more recent and NHS-relevant utility data for palliative care, the EAG preferred applying a multiplier of 0.95 (representing the ratio of

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progression-free and progressed disease utility estimated from PROpel in TA951) to the company's estimate for progression-free survival utility from TALAPRO-2 for the entire health state. The committee was concerned that in the company's model, the low palliative care utility value was applied for too long. The committee concluded that in the absence of a plausible approach for using post-progression and palliative care utility values, it preferred the EAG's approach of using a single value for the full post-progression health state. But it would consider alternative scenarios if these were generalisable to current NHS practice.

After consultation, the company agreed with using a single utility value for the full post-progression health state. It stated that a utility value of 0.70 is appropriate to use in its base case. This is because its model used the average utility for a healthy male around the average age used in the model, which is about 0.78. So, it considered that 0.775 is too high and too close to the general population utility estimate. The company noted that 0.70 is in the middle of the plausible range of published estimates (0.65 to 0.775). Also, that the EAG utility is towards the higher end of the plausible range and may bias against talazoparib with enzalutamide. It explored alternative post-progression scenarios that included palliative care utilities. After consultation, the EAG agreed that the progressed disease utility from PROpel of 0.775 is the top end of the plausible range, because it is relatively close to progression-free values. It noted that the literature review by Castro et al. (2025) reported a pooled post-progression utility estimate of 0.70 but this did not include the post-progression utility from PROpel, which would increase this estimate. So, the EAG considered that the company's utility of 0.70 is reasonable but the plausible range could be between 0.70 and 0.775. The committee acknowledged the company's concerns about using a utility value of 0.775. But it agreed that using a

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utility value from a similar trial population to TALAPRO-2 provides a more reliable estimate compared with an arbitrary midpoint value from the literature. So, it agreed to use a post-progression utility of 0.775.

Costs

Drug wastage costs

3.14 The company assumed drug wastage costs for intravenous drugs because some of the drugs may be wasted if vial sharing practices are not in place. But no wastage costs were assumed for oral treatments and the costs for the exact number of tablets or capsules needed for treatment were included in the model. The company did provide a scenario in which drug wastage costs were assumed for both intravenous and oral treatments. The EAG preferred this approach in its base case. The committee concluded that full drug wastage costs should be included in the base case.

Post-progression costs

3.15 For the progressed health state in the model, the company applied end of life care costs from TA951 and palliative care costs from a UK-specific prostate cancer source (Round et al. 2015). The EAG advised that applying both end of life care and palliative care costs would be double counting, and it preferred to only include the palliative care cost from Round et al. (2015) in its base case. The committee concluded that it was satisfied with the EAG's assumption of only applying the palliative care costs.

Severity

3.16 NICE's methods on conditions with a high degree of severity did not apply.

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Other factors

Equality

3.17 The committee noted that some people with untreated hormone-relapsed metastatic prostate cancer may be older or from a Black ethnic group. People from an Ashkenazi Jewish ethnic background have a higher risk of having a BRCA mutation, so have a higher risk of prostate cancer. Some people with hormone-relapsed metastatic prostate cancer identify as non-binary or are trans. Age, race and gender reassignment are protected under the Equality Act 2010. The committee noted that differences in incidence and prevalence cannot be addressed in a technology appraisal. Because its recommendation does not restrict access to treatment for some people over others, based on the protected characteristics, the committee concluded that these were no potential equalities issues.

Uncaptured benefits

3.18 The committee considered whether there were any uncaptured benefits of talazoparib plus enzalutamide. The committee asked the clinical experts if corticosteroid exposure is a key concern for this population. The clinical experts advised that corticosteroid exposure could impact some people because they are unable to tolerate corticosteroids (see section 3.2). The committee acknowledged that lack of corticosteroid exposure is an additional benefit of talazoparib plus enzalutamide that is not captured in the economic modelling if considering a recommendation for the whole population, but not when considering talazoparib plus enzalutamide in a population of people who cannot have abiraterone. As discussed in section 3.12, the committee agreed to exclude the cost and disutility associated with skeletal-related events from the economic model base case. This was because it considered these as a potential uncaptured benefit of talazoparib plus enzalutamide. So, the committee took these into consideration for its decision making.

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Cost-effectiveness estimates

Acceptable ICER

3.19 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. At the first meeting the committee noted the high level of uncertainty, specifically that:

- all comparators had not been modelled and a fully incremental analysis was not provided (see section 3.3 and section 3.7)
- there were limitations in all of the indirect comparison approaches; specifically, the unanchored MAIC used in the base case was very uncertain (see section 3.7)
- the modelling of time on treatment was inconsistent across the treatment arms (see section 3.11)
- 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 (see section 3.13).

At the second meeting, the company provided a fully incremental analysis that used the committee's preferences on utility values from the first committee meeting. But the uncertainties around the indirect comparisons remained. The committee noted that the cost-effectiveness estimates for talazoparib plus enzalutamide for the full marketing authorisation population exceeded the maximum cost-effectiveness thresholds for decision making. The committee agreed that it was relevant to consider an optimised population presented by

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the company as its base case and suggested by stakeholders during consultation on the draft guidance; that is, people for whom abiraterone is unsuitable or not tolerated. The committee decided there was lower uncertainty in the evidence for the optimised population because the data informing the modelling was from TALAPRO-2, which was a direct comparison of talazoparib with enzalutamide and enzalutamide plus placebo. The committee noted that for people with hormone-relapsed metastatic prostate cancer for whom abiraterone is unsuitable or is not tolerated there:

- is unmet need for first-line treatments because of the lack of treatment options with multiple mechanisms of action (see section 3.2)
- are potential uncaptured benefit of improvements in disease control from excluding skeletal-related events in the modelling (see section 3.18).

The committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Cost-effectiveness estimates

3.20 Because of confidential commercial arrangements for talazoparib, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. The committee's preferred assumptions were to:

- consider an optimised population of people with untreated hormone-relapsed metastatic prostate cancer when chemotherapy is not yet clinically indicated and abiraterone is not tolerated, or there are clinical conditions that preclude the use of treatments with abiraterone (see section 3.3)

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- extrapolate OS data for talazoparib plus enzalutamide and enzalutamide using a generalised gamma distribution and rPFS using a gamma distribution (see section 3.10)
- assume time to treatment discontinuation from TALAPRO-2 (see section 3.11)
- exclude skeletal-related events for all treatment arms and consider it as an uncaptured benefit (see section 3.12)
- use a post-progression utility of 0.775 (see section 3.13)
- fully apply drug wastage costs (see section 3.14)
- exclude end of life care costs and only include palliative care costs (see section 3.15).

Conclusion

Recommendation

3.21 The committee recognised that talazoparib plus enzalutamide is an effective treatment in terms of rPFS and OS compared with enzalutamide monotherapy. The cost-effectiveness estimates for talazoparib with enzalutamide compared with enzalutamide alone in the optimised population, when abiraterone is not tolerated or there are clinical conditions that preclude the use of abiraterone with prednisolone, are within the range that NICE considers an acceptable use of NHS resources. So, talazoparib with enzalutamide can be used as an option for untreated hormone-relapsed metastatic prostate cancer in adults when chemotherapy is not clinically indicated and abiraterone is not tolerated, or there are clinical conditions that preclude the use of abiraterone plus prednisolone.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards,

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NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated hormone-relapsed metastatic prostate cancer when chemotherapy is not clinically indicated and there are clinical conditions that preclude the use of abiraterone, and the healthcare professional responsible for their care thinks that talazoparib

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with enzalutamide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Dr Charles Crawley

Chair, technology appraisal committee B

NICE project team

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

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ISBN: [to be added at publication]

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