National Institute for Health and Care Excellence

Health Technology Evaluation

Talazoparib with enzalutamide for untreated hormone-relapsed metastatic prostate cancer [ID4004]
Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Pfizer	We consider that a cost-comparison approach for this appraisal is the most appropriate and proportionate approach. The cost-comparison analysis will assume clinical similarity in both efficacy and safety between Talazoparib plus Enzalutamide and Olaparib plus Abiraterone as supported by the literature, clinical expert opinion and an indirect treatment analysis.	Thank you for your comment. No action required.
	Prostate Cancer UK	Prostate cancer UK welcomes the evaluation of talazoparib used in conjunction with enzalutamide for untreated, metastatic hormone-resistant prostate cancer. There are several treatments available in the metastatic castrate resistant setting, such as docetaxel, abiraterone, enzalutamide, or cabazitaxel. We also note that this proposed combination comes in the context of a shifting treatment landscape for mCRPC with recent approval of abiraterone and olaparib TA951 Olaparib is available as a monotherapy for patients with a BRCA variant, or available as a combination therapy with abiraterone for men	Thank you for your comment. No action required.

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		who have previously been untreated. Radium 223 is a further last line treatment.	
	British Uro-oncology Group	This represents a drug combination with synergistic mechanism of action in the management of mCRPC patients with HRR mutations. Represents a potential new treatment option in group of patients developing mCRPC with HRR mutations who have previously not had Enzalutamide in the MHSPC setting. Agree with STA as the evaluation route	Thank you for your comment. No action required.
Wording	Pfizer	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes	No action required.
	Prostate Cancer UK	Prostate cancer UK believes the wording is reflective of the issues of the clinical and cost effectiveness.	No action required.
	British Uro-oncology Group	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes	No action required.
Timing Issues	Pfizer	The timing of the appraisal is appropriate.	No action required.
	Prostate Cancer UK	Patients who are considered to be in this indication, especially those in this indication who are also contra-indicated to docetaxel, and also abiraterone, prednisolone, or olaparib and thus would not be eligible to have these as	Thank you for your comment. NICE has scheduled this topic into its work programme.

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		alternative treatment options, could benefit from talazoparib with enzalutamide and it's subsequent increase in progression free survival. We also would suggest that those patients with more aggressive prostate cancers would benefit from a more urgent approach to this evaluation, as this would allow this drug combination to be available faster to those who may be facing a shorter timeframe to progression and possible death from their prostate cancer. It is imperative for these patients to receive the best standard of care in a timely fashion which would allow for the longest potential time to progression	For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-ta10904
	British Uro-oncology Group	This combination has been tested in phase 3 trial and has shown benefit in all comers and in patients with HRR alterations. It has been approved by FDA and is available in healthcare in some other countries. Given limited options in patients with mCRPC not eligible for chemotherapy, this combination should be evaluated promptly.	Thank you for your comment. NICE has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-ta10904
Additional comments on the draft remit	Pfizer	No comment.	No action required.
	Prostate Cancer UK	No comment.	No action required.
	British Uro-oncology Group	No comment.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	We agree with the accuracy of the background information.	No action required.
	Prostate Cancer UK	We consider the background information to be sufficient.	No action required.
	British Uro-oncology Group	The information presented is accurate and complete	No action required.
Population	Pfizer	The population is defined appropriately.	No action required.
	Prostate Cancer UK	In clinical practice we expect patients to have previously been treated with docetaxel or a NHA by the time they become metastatic hormone sensitive. More clarity is needed on patients previously treated with enzalutamide in that setting, or indeed patients treated with abiraterone in the non-metastatic setting and whether they would be eligible for this combined treatment. Current policy only allows for treatment with one novel hormonal agent, but it isn't clear if this also applies to combination therapies such as this. Because of the Covid-19 pandemic many patients will have been receiving enzalutamide as an alternative to chemotherapy and so many may not be eligible.	Thank you for your comment. The appropriate population will be decided according to the company's marketing authorisation, and NHS practice.
	British Uro-oncology Group	*Is the population defined appropriately?* Yes	No action required.
Subgroups	Pfizer	No sub-group consideration is required for the technology. Talazoparib with Enzalutamide is considered clinically comparable to Olaparib with Abiraterone and is likely to be used in the same population in clinical practice.	Thank you for your comment. The scope specifies that if evidence allows, those

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			subgroups will be considered by company. The company submission provides an opportunity for you to present these analyses or to provide a rationale for deviating from the scope. No action required.
	Prostate Cancer UK	Median time to initiation of cytotoxic chemotherapy and time to initiation of subsequent antineoplastic therapy are not yet available for TALAPRO-2 but examination of data by subgroups may help inform clinicians and NICE on the most suitable candidates that are most likely to benefit from this treatment combination in terms of delaying need for subsequent therapy or chemotherapy and associated side effects.	Comment noted. Where evidence allows, the cost-effectiveness of the technology in relevant subgroups will be considered by the committee during appraisal.
	British Uro-oncology Group	The combination has shown efficacy in all comers (in those with and without HRR alterations) and can be considered in all comers.	Comment noted. Where evidence allows, the cost-effectiveness of the technology in relevant subgroups will be considered by the committee during appraisal.

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Comparators	Pfizer	Olaparib with abiraterone represents the only relevant comparator for this cost comparison submission. Although enzalutamide monotherapy and abiraterone monotherapy are also in the same position in the treatment pathway as talazoparib with enzalutamide and olaparib with abiraterone, they are not relevant to this cost comparison appraisal because cost-effectiveness of olaparib with abiraterone was demonstrated against both enzalutamide monotherapy and abiraterone monotherapy in TA951. Given that talazoparib with enzalutamide provides similar or greater health benefits at similar or lower costs than olaparib with abiraterone, a comparison versus enzalutamide and abiraterone is therefore not required.	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison.
	Prostate Cancer UK	Additional comparisons may include Olaparib monotherapy and Talazoparib (data from TALAPRO-1), through network meta-analyses such as here, in the absence of crossover treatment with PARP inhibitor in control arm. Moreover, only 17% patients received subsequent PARP inhibition as indicated by Bono, J, et al (2023), this will mean that overall survival data (when released – still immature) cannot be used to support radiographic progression data as controls may be biased towards death.	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison. Talazoparib monotherapy has not been included as a comparator in this appraisal because it is not part of established practice in the NHS. Olaparib monotherapy is recommended in TA887 as an option for treating hormone-relapsed metastatic

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			prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) in adults. But retreatment with newer hormonal treatment is not permitted in UK clinical practice. So it is highly unlikely that olaparib monotherapy (which requires prior newer hormonal treatment) is a comparator for talazoparib with enzalutamide.
	British Uro-oncology Group	In the setting of all comers, the comparators will be Abiarterone, Enzalutamide, Abiraterone+Olaparib combination In the setting of patients with HRR alterations, Olaparib alone should also be a comparator	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison. Olaparib monotherapy is recommended in TA887 as an option for

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			treating hormone-relapsed metastatic prostate cancer with BRCA1 or BRCA2 mutations that has progressed after a newer hormonal treatment (such as abiraterone or enzalutamide) in adults. But retreatment with newer hormonal treatment is not permitted in UK clinical practice. So it is highly unlikely that olaparib monotherapy (which requires prior newer hormonal treatment) is a comparator for talazoparib with enzalutamide.
Outcomes	Pfizer	*Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?* Yes	No action required.
	Prostate Cancer UK	Prostate Cancer UK believes the outcomes are appropriate	No action required.

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	British Uro-oncology Group	Yes, they are appropriate	No action required.
Equality	Pfizer	The Current Standard of Care (Olaparib plus Abiraterone) for patients who are eligible for a PARPi + NHT combination includes Prednisolone (steroid) as one of the treatment components. This combination poses the risk of steroid exposure which is difficult for a set of population. Additionally, Abiraterone is not the first choice option NHT for many patients, so a combination containing a different NHT (Enzalutamide) and without Prednisolone promotes equality and ensure all eligible patients have access to a PARPi combination. Around 1 in 6 men develop prostate cancer and this disproportionately affects men of black ethnicity – around 1 in 4 black men will develop prostate cancer	Thank you for your comment. We have added your comments to the Equality Impact Assessment form. Equality and diversity will be considered by the appraisal committee when formulating its recommendations.
	Prostate Cancer UK	We welcome inclusion of Black men in this trial and note that in UK population, around 4% of men in UK are of Black African, Black Caribbean and Black other (ONS 2021). In analysis of the treatment arm of TALAPRO-2 trial, 3% of Black or African American were included, similar to PROpel trial arms. However, we note that in the control arm of TALAPRO-2 this drops to 1%. In general, greater representation of men from ethnic minority backgrounds including Black men is needed to find out if results are generalisable, especially given findings that DNA repair genes other than BRCA1/2 variants may play a greater role in increasing Black men's risk of prostate cancer than of white men of European ancestry so understanding the relative efficacy of different drug combinations on this sub population is important (here).	Thank you for your comment. We have added your comments to the Equality Impact Assessment form. Equality and diversity will be considered by the appraisal committee when formulating its recommendations.
	British Uro-oncology Group	There appears no discrimination	Thank you for your comment. Equality and diversity will be

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			considered by the appraisal committee when formulating its recommendations.
Other considerations	Pfizer	No comment.	No action required.
	Prostate Cancer UK	Difficult questions remain on best use of PARPi and ARSI in metastatic prostate cancer setting, as either first line or second line therapy and their tolerability, although recent meta-analysis has supported combination therapy in first line setting (here). In the TALAPRO-2 trial, side effects are notable, particualrly in regards to anaemia. There was 2.7 times higher risk of anaemia across all grades and an even higher risk among grade >= 3, when taking talazoparib and enzalutamide as a combination compared to control. In grade >=3, the proportion of men suffering from anaemia in treatment arm (46%) is also much greater than in control arm (4%). Moroever, when compared to abiraterone and olaparib, we noted there was also an increased risk of anaemia in 'all grade' patients taking talazoparib and enzalutamide than in all grade patients in PROpel taking olaparib and abiraterone. Furthermore, the proportion of participants affected by anaemia among >3 grade patients was comparatively high for patients in TALAPRO-2 trial who received talazoparib and enzalutamide (46%) vs Olaparib and abiraterone in PROpel trial (15.1%). However, we note that i) around half of participants (49%) in TALAPRO-2 trial treatment arm had baseline grade 1-2 anaemia ii) serious side effects were roughly similar across TALAPRO-2 treatment arm (39%) and PROpel treatment arms (33.9%) and that iii) only 33 patients (8%) discontinued talazoparib because of anaemia. Nonethless it is important to consider that	Thank you for your comment. The appropriate population will be decided according to the company's marketing authorisation, and NHS practice.

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		disontinuation rate may be even greater outside of trial setting where dose control may not be as easy to manage.	
	British Uro-oncology Group	Need to consider resources for testing for HRR alterations	Thank you for your comment. The scope includes the following instruction: The economic modelling should include the cost associated with diagnostic testing for people with hormone-relapsed metastatic prostate cancer who would not otherwise have been tested. No action required.
Questions for consultation	Pfizer	**Where do you consider talazoparib with enzalutamide will fit into the existing care pathway for adults with untreated hormone-relapsed metastatic prostate cancer?** First-line treatment options for mCRPC patients for whom chemotherapy is not indicated includes enzalutamide (TA377), abiraterone (TA387), and, since February 2024, olaparib with abiraterone (TA951). The licensed indication for talazoparib with enzalutamide is for the treatment of adults with hormone-relapsed metastatic prostate cancer for whom chemotherapy is not clinically indicated. As such, the proposed position of	Thank you for your comment. No action required.

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		talazoparib with enzalutamide is alongside olaparib with abiraterone, enzalutamide, and abiraterone as first-line treatment options for mCRPC. **Please select from the following, will talazoparib with enzalutamide be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** NA **Are there any testing costs related to this treatment or disease that should be included in the economic modelling?** No **Would talazoparib with enzalutamide be a candidate for managed access?** No **Do you consider that the use of talazoparib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** As we are conducting a cost comparison analysis, there will be no QALY calculation. There are no further substantial health-related benefits to be included.	

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		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. • Published trial data (Talapro-2, Agarwal et.al. 2023) • Systematic Literature review & Network meta-analyses • Cost-comparison model	
	Prostate Cancer UK	Given that recently abiraterone has gone off-patent, does this mean that talazoparib and enzalutamide are economically less cost effective than Olaparib and abiraterone within the same indication? Moreover, it is interesting to note that market authorisation and approval by FDA of talazoparib and enzalutamide was specifically for HRRm patients in first line setting due to superior efficacy of this combination in BRCA variants and favourable OS (immature results) in HRRm subgroup (compared to all comers). This raises the question of whether the potential option of talazoparib and enzalutamide means that we need increased testing capacity to conduct HRRm genetic testing in men with metastatic prostate cancer (for which there is some guidance) to help clinicans make informed choice on whether this combination is favourable over abiraterone and olaparib combination?	Comment noted. The appraisal committee will discuss the potential of this technology to be cost effective. Where evidence allows, the cost-effectiveness of the technology in relevant subgroups will also be considered by the committee during appraisal. No action required.
	British Uro-oncology Group	No comment.	No action required.
Additional comments on the draft scope	Pfizer	No comment.	No action required.
	Prostate Cancer UK	No comment.	No action required.

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	British Uro-oncology Group	No comment.	No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A