National Institute for Health and Care Excellence

Health Technology Evaluation

Darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer ID6452

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	Bayer	Bayer is proposing a cost-comparison approach for this appraisal, and that darolutamide is evaluated against an existing NICE-recommended treatment option within the same class. Darolutamide and apalutamide, represent a group of novel non-steroidal anti-androgens characterised by higher affinity for the androgen receptor (AR) compared to traditional non-steroidal anti-androgens. Unlike earlier agents, which permitted AR transfer to the nucleus and could act as partial agonists, both therapies also block AR nuclear transfer, thereby eliminating any potential agonist-like activity. Initial results from an indirect treatment comparison suggest that darolutamide and apalutamide demonstrate comparable efficacy in the treatment of prostate cancer. This finding has gained further support following discussions at a recent UK advisory board, where leading clinicians carefully	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison.

Section	Stakeholder	Comments [sic]	Action
		reviewed the available data. The clinicians not only acknowledged the comparable effectiveness of the two treatments but also emphasised the same place in the treatment pathway for patients with mHSPC. Given the comparable effectiveness, shared mechanisms of action, and identical place within the treatment pathway, suggests that a cost-comparison approach would be a suitable and appropriate method for this appraisal.	
	Prostate Cancer Research	The route is appropriate.	Thank you for your comment. No action required.
	Prostate Cancer UK	Prostate cancer UK welcomes the evaluation of darolutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer. There are several treatments available in the metastatic hormone sensitive setting, such as ADT alone, enzalutamide plus ADT, apalutamide plus ADT, darolutamide triplet therapy and docetaxel plus ADT. However, there still remains a strong need for further treatments in this indication that offer good clinical benefit and improvement in progression free survival. It is clear from the evidence in the ARANOTE trial that this drug combination could fit this remit. Should the proposed appraisal recommend that darolutamide with ADT is effective for the above indication, it will increase treatment choice for a group of patients who currently still have a restricted range of treatments available. This will allow for a more tailored approach to a patient's prostate cancer treatment by taking their individual needs and preferences into account when developing a treatment plan. We believe that the single technology appraisal route is appropriate in this instance.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
	Tackle Prostate Cancer	It would be logical now to include the combination of Darolutamide and ADT as a potential treatment for hormone sensitive metastatic prostate cancer. Other similar doublet therapies have already been approved in this clinical situation. Approval of Darolutamide/ADT combination will allow use in patients who have co-morbidities which make them unsuitable for other similar treatments. The good side effect profile of Darolutamide have been established at other appraisals.	Thank you for your comment. No action required.
Wording	Bayer	Yes, the wording of the remit reflects the issues of clinical and cost-effectiveness for this technology.	Thank you for your comment. No action required.
	Prostate Cancer Research	Yes	Thank you for your comment. No action required.
	Prostate Cancer UK	To the best of our knowledge the wording of the remit reflects the clinical and cost effectiveness issues.	Thank you for your comment. No action required.
	Tackle Prostate Cancer	It is not really within the remit of a patient organisation to comment on cost effectiveness. However if a treatment compares favourably both in cost and clinical effectiveness with other similar therapies it would seem illogical not to approve them.	Thank you for your comment. No action required.
Additional comments on the draft remit	Bayer	No additional comments on the draft remit	Thank you for your comment. No action required.

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	Prostate Cancer Research	Nil.	Thank you for your comment. No action required.
	Prostate Cancer UK	N/A	No action required.
	Tackle Prostate Cancer	N/A	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bayer	No comments	Thank you for your comment. No action required.
	Prostate Cancer Research	While mentioning environmental and genetic factors is correct, the term "unknown" is overly simplistic. Adding examples such as BRCA2 mutations or lifestyle factors (e.g., diet, obesity) would provide more depth. The projection of a 15% increase in prostate cancer incidence rates (2023–2025) lacks context, such as potential reasons for this rise (e.g., aging population or increased screening).	Thank you for your comment. The background section of the scope provides a brief overview of the disease. More detailed information will be explored at the submission stage.

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		Mortality data (age-standardized rate) is cited for 2021 but could include survival trends or improvements over time to contextualize the impact of treatments. The overview could benefit from mentioning ongoing areas of research or treatment challenges, such as the role of biomarkers, patient stratification, or the impact of treatment on quality of life. Bone metastases are common in metastatic prostate cancer. Mentioning therapies for bone health management would round out the treatment landscape. It would also be good to addressing the importance of patient preferences.	Some changes have been made to the background section.
	Prostate Cancer UK	We consider the background information to be sufficient.	Thank you for your comment. No action required.
	Tackle Prostate Cancer	Good	Thank you for your comment. No action required.
Population	Bayer	Bayer considers the population for this submission will consist of people with hormone-sensitive metastatic prostate cancer **who are unsuitable for chemotherapy.** Darolutamide in combination with ADT and docetaxel has been recommended by NICE. Therefore, the scope of this appraisal will specifically focus on patients ineligible to receive chemotherapy.	Thank you for your comment. No action required. The committee will only be able to make recommendations within the marketing authorisation for this technology. The committee will consider if it is appropriate to

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			make a recommendation for a narrower population.
	Prostate Cancer Research	Yes	Thank you for your comment. No action required.
	Prostate Cancer UK	We believe the population is defined appropriately.	Thank you for your comment. No action required.
	Tackle Prostate Cancer	Yes	Thank you for your comment. No action required.
Subgroups	Bayer	**People with newly diagnosed metastatic prostate cancer** Both patients with M1 (de novo) and M0 (recurrent) at initial diagnosis have been included in ARANOTE. The majority of patients **(72.5%)** were de novo and the results in ARANOTE have been consistent across these subgroups. Therefore, Bayer believes the appraisal should be focused on the ITT population Consistency between these subgroups gives further re-assurance that darolutamide is similarly efficacious in both newly diagnosed de novo patients and patients with mHSPC in general. We suggest removing this subgroup from the scope.	Thank you for your comment. The scope specifies that if evidence allows, those subgroups will be considered by company. The company submission provides an opportunity to present these analyses or to provide a rationale for deviating from the scope. No action required.

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		People with high-risk metastatic prostate cancer It is not clear what the high-risk metastatic prostate cancer definition is in the scope. ARANOTE has been stratified by extent of disease (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). The efficacy observed in ARANOTE was consistent across these three subgroups. There was no classification by 'high-risk' disease in ARANOTE. We suggest removing this subgroup from the scope. There is inconsistent use of 'newly diagnosed' and 'high risk' for randomisation across all mHSPC trials. These sub-populations would be most relevant to abiraterone, which is specifically licensed for use in newly diagnosed high risk population. However, abiraterone is not a relevant comparator in this appraisal as it has not been currently approved for use in NHS practice. We believe the subgroups suggested in the scope are not appropriate for this appraisal and should be removed.	
	Prostate Cancer Research	Noting that subgroups will be considered if the evidence allows, it would be helpful in the background information to group therapies for clarity (into those specifically as first line options for the newly diagnosed and high risk metastatic).	The background section of the scope provides a brief overview of the treatments available. More detailed information will be explored at the submission stage.

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	Prostate Cancer UK	We believe it would be useful to define the population who would most benefit from this doublet regimen versus other doublet treatments and darolutamide triplet treatment. We have elaborated on this within the “other considerations” section. However, we do also note that dividing the population into subgroups could introduce uncertainty into the cost-effectiveness analysis of the treatment that may ultimately result in some patients unfairly missing out. The committee may want to consider this when deciding whether subgroup analysis would be beneficial in this case.	Thank you for your comment. No action required.
	Tackle Prostate Cancer	Subgroups as stated in the draft scope are appropriate	Thank you for your comment. No action required.
Comparators	Bayer	As Bayer is proposing a cost-comparison approach for this appraisal, we believe the appropriate comparator for this appraisal is apalutamide in combination with ADT. Apalutamide is currently recommended by NICE as a treatment option for patients with mHSPC who are unsuitable for chemotherapy (NICE TA741). Similarly, the target population for darolutamide in combination with ADT would also be patients with mHSPC who are unsuitable for chemotherapy. Therefore, we consider apalutamide + ADT to be the only relevant comparator for this appraisal.	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison.
	Prostate Cancer Research	Other Androgen Receptor Inhibitors are the most relevant comparators.	Thank you for your comment. The scoping comparators have been narrowed to only those

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			that are appropriate for cost comparison.
	Prostate Cancer UK	Yes, all comparators listed are considered to be the standard treatments currently used within the NHS. All relevant comparators have been included.	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison.
	Tackle Prostate Cancer	It would be illogical to use *triplet* therapy as a direct comparator for this appraisal of *doublet* therapy - this is not a direct comparison of similar therapies. Doublet therapy combining ADT and enzalutamide / apalutamide / abiraterone is now standard of care in newly diagnosed hormone sensitive metastatic prostate cancer. The use of ADT alone would now be considered as substandard care and should therefore not be a direct comparator. The clinical effectiveness and safety of darolutamide has already been established in other appraisals.	Thank you for your comment. The scoping comparators have been narrowed to only those that are appropriate for cost comparison.
Outcomes	Bayer	Bayer proposes the following outcome measures to capture the most important health benefits for darolutamide: • **Radiographic** progression free survival • Overall survival • **Time to castration resistant prostate cancer** • **Time to subsequent therapy** • Prostate-specific antigen ~~response~~ **undetectable rate** • Time to prostate-specific antigen progression • Adverse effects of treatment • Health-related quality of life.	Thank you for your comment. The outcomes in the scope have been updated. The list of outcomes presented presents a summary of the main outcomes and is not intended to be an exhaustive list. The company is invited to include the outcomes

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		Bayer proposes that “response rate” be removed from the list of outcomes as it is not generally used as an outcome measure in advanced prostate cancer as prostate metastases, particularly bone metastases, generally do not show radiological responses to treatment, even though overall the treatment may be working.	commonly used in clinical practice in hormone sensitive prostate cancer within its evidence submission.
	Prostate Cancer Research	Time to castration resistance and time to pain progression might usefully be added.	Thank you for your comment. The outcomes in the scope have been updated. The list of outcomes presented presents a summary of the main outcomes and is not intended to be an exhaustive list. The company is invited to include the outcomes commonly used in clinical practice in hormone sensitive prostate cancer within its evidence submission.
	Prostate Cancer UK	Prostate Cancer UK believes the outcomes are appropriate.	Thank you for your comment. No action required.

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	Tackle Prostate Cancer	Yes	Thank you for your comment. No action required.
Equality	Bayer	No comments	Thank you for your comment. No action required.
	Prostate Cancer Research	Nil.	Thank you for your comment. No action required.
	Prostate Cancer UK	We welcome the inclusion of Black men in this trial and note that they represented around 10% of the total trial population.	Thank you for your comment. The committee will consider any relevant equality issues when it makes recommendations. The equality issues raised have been formally considered in the equality impact assessment. The scope notes that the incidence of prostate cancer is higher in people of a black African-Caribbean origin. No action required.

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	Tackle Prostate Cancer	There are no equality issues that could be to the detriment of some patient groups. Indeed allowing darolutamide to be used as tablet therapy in this context would allow patients unsuitable for other potential treatments to be appropriately managed.	Thank you for your comment. No action required.
Other considerations	Bayer	No additional issues have been identified.	Thank you for your comment. No action required.
	Prostate Cancer Research	Nil.	Thank you for your comment. No action required.
	Prostate Cancer UK	There is only indirect evidence available due to a lack of head-to-head trial data between those taking other androgen receptor signalling inhibitor drug-based treatment such as abiraterone/enzalutamide and ADT versus those taking Darolutamide and ADT (1) (2)(3)(4). It is important to note that the ARANOTE trial (5) excluded men who were treated with chemotherapy and the submitting company views this population of men as separate to those eligible for triplet therapy, with the intention to provide patients with greater choice and potentially gentler drug regimen with past metanalysis indicating fewer adverse events associated with Darolutamide than other androgen receptor signalling inhibitor drugs i.e. there is potential for use in men with poor cardiovascular and bone health (5) This choice may prove vital for some men given the disparity between NICE recommendation for use of docetaxel, and uptake in England and Wales, with recent evidence (2019-2023) that use of docetaxel in England and Wales is only at 37% (6) for diagnosed men starting systemic therapy and between 30-	Thank you for your comment. No action required.

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		40% (2019-2020 data) (7) for those diagnosed with metastatic hormone sensitive prostate cancer. A recent review has also highlighted inequalities with respect to the use of triplet therapy, impacted by factors such as age, ethnicity and those living within urban settings (8) However, further evidence is required to more clearly define the population who would most benefit from this doublet regimen versus other doublet treatments and triplet treatment. This is important to consider as there is evidence to suggest that i) the use of docetaxel may be highly efficacious in high volume disease ii) ARANOTE trial results suggest improved efficacy particularly in low volume setting and iii) Darolutamide based treatment demonstrates potential use particularly for subgroup of men with Gleason ≥8 (1). Moreover, the long-term impact of using Darolutamide and ADT as a first line treatment in this setting and on treatment options on disease progression are not defined. Final results on overall survival (which are not yet available via ARANOTE trial) may help us to better understand long-term impact of the proposed drug combination in mHSPC setting.	
	Tackle Prostate Cancer	N/A	No action required.
Questions for consultation	Bayer	**Where do you consider darolutamide with androgen deprivation therapy will fit into the existing care pathway for hormone-sensitive metastatic prostate cancer?**	Thank you for your comment. No action required.

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		Bayer anticipates that darolutamide + ADT will serve as an additional treatment option for patients with metastatic hormone-sensitive prostate cancer (mHSPC) who are unsuitable for chemotherapy. Despite the availability of second-generation ARIs such as enzalutamide and apalutamide, data from UK clinicians estimates ADT monotherapy to be between 30-50%. This persists despite guideline recommendations advocating for treatment optimisation, highlighting an unmet need for efficacious and tolerable treatment options in this population. Not all patients with mHSPC are eligible for chemotherapy, with age being a significant determinant of eligibility. Older patients are notably less likely to receive chemotherapy compared to younger age groups. A 2016 report by Prostate Cancer UK revealed that only 64% of patients under 70 diagnosed with metastatic disease received chemotherapy. Older and frailer patients, in particular, may not be suitable for triplet therapy with darolutamide, docetaxel, and ADT. This creates an unfair disadvantage for older patients, who are less likely to be eligible for chemotherapy and, as a result, face poorer clinical outcomes. Offering darolutamide + ADT as an additional treatment option would provide clinicians with greater flexibility to tailor therapies to the individual needs of their patients. This is particularly important for the disadvantaged older population, enabling access to a more effective treatment alternative and offering the best chance of improving survival outcomes. Please select from the following, will darolutamide with androgen deprivation therapy 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**	

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		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. Darolutamide is currently prescribed in secondary care with follow-up in secondary for its existing indications, including mHSPC in combination with docetaxel and ADT, as well as non-metastatic castration-resistant prostate cancer in combination with ADT. This prescribing and care model will remain unchanged for this new indication, ensuring no additional service changes are required. This approach aligns with the established prescribing patterns of its comparator, apalutamide. **Would darolutamide with androgen deprivation therapy and docetaxel be a candidate for managed access?** It is anticipated that the current evidence for darolutamide+ ADT will support decision for routine commissioning, therefore it is not anticipated that darolutamide + ADT will be a candidate for managed access. **Do you consider that the use of darolutamide with androgen deprivation therapy can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Darolutamide's molecular structure has been shown to have limited drug-on-drug interactions (DDIs) when compared to other novel anti-hormonal agents. These interactions are important considerations in clinical practice and can have an impact on concomitant medication efficacy and prescribing and hence the survival of patients and their quality of life, as well as on the monitoring capacity of clinicians, but are difficult to capture robustly in the cost-effectiveness/comparison framework. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits**.	

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		Published evidence has shown darolutamide to have limited potential for clinically relevant DDIs with co-medications frequently used to treat age-related comorbidities (such as hypertension, diabetes, cardiovascular disease, kidney disease, etc.) in patients with prostate cancer.[1,2,3] It has also been shown to cause less frequent severe DDIs when compared to other novel anti-hormonal agents;[4] as unlike other novel antihormonal agents, no clinically relevant drug-drug interaction is expected in case of CYP3A4, P-gp, BCRP, UGT1A9 inhibitor administration, or P-gp and CYP substrate administration with darolutamide.[5] Although DDI are clinically significant when selecting a treatment, quantifying their impact and incorporating them into a cost-comparison is challenging. This is primarily due to the limited availability of data connecting these interactions to definitive clinical outcomes or cost implications.	
	Prostate Cancer Research	Nil.	Thank you for your comment. No action required.
	Prostate Cancer UK	N/A	No action required.
	Tackle Prostate Cancer	N/A	No action required.
Additional comments on the draft scope	Bayer	No additional comments	Thank you for your comment. No action required.

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	Prostate Cancer Research	Nil.	Thank you for your comment. No action required.
	Prostate Cancer UK	N/A	No action required.
	Tackle Prostate Cancer	N/A	No action required.

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

Astellas Pharma Ltd

AstraZeneca

IPSEN Limited

Royal College of Pathologist