National Institute for Health and Care Excellence

Health Technology Evaluation

Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer (ID3971)

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Bayer	Bayer considers the route proposed (single technology appraisal) to be appropriate	Thank you for your comment. No action required.
	Tackle Prostate Cancer	This certainly a topic that is of interest to patients with a diagnosis of hormone sensitive prostate cancer – particularly those who are newly diagnosed and already have metastatic disease. Many at this stage can be relatively young in age and anxious to receive the maximum and most effective therapy available. They may also have few or no co-morbidities and able to withstand the potential rigours of multiple drug therapy. I am unable to comment on the evaluation route proposed except to say that all other appraisal with which I have been involved have been single technology appraisals.	Thank you for your comment. No action required.

	Prostate Cancer UK	Prostate Cancer UK welcomes the evaluation of Darolutamide with androgen deprivation therapy and docetaxel for treating hormone-sensitive metastatic prostate cancer. We also believe that the single technology appraisal route is the appropriate evaluation route for this treatment. We recognise that there are treatment options already available in this area such as such as androgen deprivation therapy (ADT) or androgen receptor pathway inhibitors plus ADT or a combination of docetaxel and ADT. However, there still remains a strong need for further treatments that offer good clinical benefit and increased survival, and it is clear from the evidence that this treatment combination could fit this remit. For example, results from the Phase III ARASENS trial showed that combining darolutamide with ADT and docetaxel increased the chance of survival and lowered the risk of death by 32.5% compared to combining ADT and docetaxel with placebo instead. Additionally, compared to patients who received the placebo, patients who received darolutamide had a delay in: their cancer becoming castration-resistant; worsening pain having cancer-related bone fractures; or related symptoms needing additional therapies for cancer.	Thank you for your comment. No action required.
Wording	Bayer	No comments	No action required.
	Tackle Prostate Cancer	No comments	No action required.
	Prostate Cancer UK	We believe that the wording reflects the clinical effectiveness issues.	Thank you for your comment. No action required.
Timing issues	Bayer	Darolutamide + docetaxel + ADT is currently undergoing accelerated licensing evaluation by MHRA via Project Orbis for use in mHSPC. The anticipated UK licensing date is [redacted]. Prioritisation of the NICE evaluation	Thank you for your comment. NICE aims to provide draft guidance

		of this technology is important in order to minimise the access gap for NHS patients from point of licensing to NICE decision for this new technology.	to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/indevelopment/gid-ta10860
	Tackle Prostate Cancer	Patients will see any potential advance in therapy to be of great importance and thus would wish appropriate new therapy to be available as soon as possible.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/indevelopment/gid-ta10860
	Prostate Cancer UK	We believe that the timing of this appraisal is appropriate. However, as the Phase III ARASENS trial has shown strong evidence of consistent benefits and increased survival rates in comparison to the comparators, we would suggest that there is a considerable level of urgency. As a Charity, we want	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6

		patients to have access to treatments that allow them to live longer as soon as possible.	months from the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. For more information please see https://www.nice.org.uk/guidance/indevelopment/gid-ta10860
Additional comments on the draft remit	Bayer	No comments	No action required.
	Tackle Prostate Cancer	No comments	No action required.
	Prostate Cancer UK	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bayer	We believe the description 'hormone-sensitive metastatic prostate cancer' refers to a population of patients that can be either newly diagnosed or relapsing from radical therapy for localised prostate cancer, who have not started or have just started androgen deprivation therapy (ADT) and whose disease continues to respond to ADT. Bayer have included both newly diagnosed (de-novo) and recurrent patients in the key phase III study ARASENS that provides the main evidence to support our regulatory and HTA submissions.	Thank you for your comment. The wording on page 2 has been updated in line with the suggested wording.

Section	Consultee/ Commentator	Comments [sic]	Action
		We suggest the following wording on page 2 of the draft scope: *The description 'hormone-sensitive metastatic prostate cancer' refers to a population that includes people with metastatic prostate cancer who have not had androgen deprivation therapy, or whose disease is continuing to respond to androgen deprivation therapy.*	
	Tackle Prostate Cancer	From a patient perspective, this seems informative and useful. However, more information on the trial outcomes would be welcomed. Most patients would not have access to any scientific data – and probably would not understand it!	Thank you for your comment. The scope aims to provide a top-line summary on the clinical trials. The evidence submissions from the stakeholders, in particular the company, will provide more commentary and discussion of the clinical trial information. We request that a simpler write-up is also provided by the company as part of its submission which will also be summarised at the committee meeting. No changes made to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
	Prostate Cancer UK	We believe that the background information in this draft remit is accurate and sufficient.	Thank you for your comment. No action required.
Population	Bayer	Bayer considers the population to be appropriate. In line with the expected license, darolutamide will be given in combination with docetaxel and ADT in patients in which docetaxel is suitable.	Thank you for your comment. No action required.
	Tackle Prostate Cancer	No comments	No action required.
	Prostate Cancer UK	We agree with the definition of the population as it will be men who have recently been diagnosed with metastatic prostate cancer and have never received (ie. are sensitive to) ADT or whose disease is continuing to respond to ADT.	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 ARASENS. The majority of patients (86%) were de novo and the results in ARASENS have been consistent across these subgroups. Therefore, Bayer believes the appraisal should be focused on the ITT population on which the ARASENS study was designed and powered to detect an effect and not give further consideration to subgroups for which the study was not powered. Consistency between these subgroups gives further re-assurance that darolutamide + docetaxel + ADT is similarly efficacious in both newly diagnosed de novo patients and patients with mHSPC in general. We suggest removing this subgroup from the scope. **People with high-risk metastatic prostate cancer**	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 for you to present these analyses or to provide a rationale for deviating from the

Section	Consultee/ Commentator	Comments [sic]	Action
		It is not clear what the high-risk metastatic prostate cancer definition is in the scope. ARASENS has been stratified by extent of disease (i.e. non-regional lymph node metastasis, bone metastasis, and visceral metastasis). The efficacy observed in ARASENS was consistent across these three subgroups. There was not classification by 'high-risk' disease in ARASENS. We suggest removing this subgroup from the scope. There is inconsistent use of 'newly diagnosed' and 'high risk' for randomisation across all mHSPC trials, and this sub-populations would be most relevant to abiraterone which is specifically licensed for this 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 and should be removed because single factors like de-novo and high-risk would not drive clinical decision in practice around the use of docetaxel. Darolutamide + docetaxel + ADT would be used in all patients eligible for chemo. Chemo (in)eligibility has been previously defined in NHSE's Commissioning Policy Statement for docetaxel and in previous appraisals (TA721, TA741) and does not relate to factors like de-novo and high-risk; i.e. people for whom docetaxel is contraindicated or unsuitable would include: • people who have contraindications to docetaxel as listed in the summary of product characteristics for docetaxel • people with poor performance status (WHO or Eastern Cooperative Oncology Group [ECOG] performance status 3 or 4, and possibly status 2 because docetaxel is used with caution in this group), which is a measure of fitness	scope. No action required.

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		• people with significant comorbidity (for example, cardiovascular, respiratory or liver disease) such that prostate cancer is not likely to be the only life-limiting illness • people with peripheral sensory neuropathy or poor bone marrow function • people with poor cognition or social support leading to a decreased ability to understand treatment options or make a decision. The population in ARASENS and the target population of the marketing authorisation does not align with the ineligibility criteria previously defined.	
	Tackle Prostate Cancer	The biggest problem is with the highly siccative group of patients in the study used. It is specifically adding Darolutamide to ADT and Docetaxel. NICE have already recognised a subgroup of men who are designated as 'chemotherapy unsuitable'. This group will NOT be able to be able to take advantage of this additional therapy. As a patient-focussed charity, Tackle strives to ensure ALL patients are treated equally. However, we would still wish to support this appraisal.	Thank you for your comment. Darolutamide will be appraised within its marketing authorisation. No action required.
	Prostate Cancer UK	We believe that the subgroups listed are appropriate for this treatment.	Thank you for your comment. No action required.
Comparators	Bayer	As also referenced in the draft scope (page 1), apalutamide plus androgen deprivation therapy (ADT) is recommended as an option for treating hormone-sensitive metastatic prostate cancer in adults, **only if docetaxel is not suitable** (NICE TA741). Docetaxel needs to be suitable by definition in all patients that would be considered candidates for darolutamide + docetaxel + ADT. Therefore, we do not consider apalutamide + ADT as a relevant comparator for darolutamide + docetaxel + ADT in this target population. This view is also aligned with clinical consensus that apalutamide + ADT should	Thank you for your comment. Apalutamide + ADT has been removed from the list of relevant comparators.

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		not be considered a relevant comparator for this appraisal as the patient populations in which clinicians would consider the use of apalutamide + ADT, in line with its restricted recommendation, and darolutamide with docetaxel and ADT are different populations which do not overlap. With the exception of apalutamide + ADT, Bayer considers the list of comparators to be appropriate for darolutamide + docetaxel + ADT. We suggest apalutamide + ADT to be removed from the list of relevant comparators in this appraisal.	
	Tackle Prostate Cancer	This a new treatment protocol involving triple therapy, and as such there is no direct comparator. Current optimal standard of care is ADT with either docetaxel or a novel hormonal agent. These would be the most likely comparators to choose. ADT alone is sub-optimal treatment but sadly many men who should be offered ADT and docetaxel do not get the opportunity. Degarelix is not widely used except in aggressive advanced PCa where spinal cord compression is deemed a possibility.	Thank you for your comment. The scope is inclusive for all comparators that are likely to be used in clinical practice. The evidence submissions can provide further commentary about the appropriateness of the comparisons specified in the scope. No changes made to the scope.
	Prostate Cancer UK	We find the comparators to be appropriate. However, it is worth noting that Apalutamide is only available to patients who can't have docetaxel and docetaxel is not always tolerated by patients who are older or who may have comorbidities and so would not be a suitable comparator for this group of patients.	Thank you for your comment. Apalutamide + ADT has been removed from the list of relevant comparators.

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Outcomes	Bayer	**Progression-free survival outcome measure that till be utilised in the appraisal:** Time to castration resistance prostate cancer (TTCRPC) in the ARASENS study 17777 is a secondary endpoint which is composed of biochemical progression and radiological progression. Imaging was to be performed on a yearly basis after the end of docetaxel treatment and in the event of signs for clinical progression at the investigator's discretion. Therefore, imaging could be performed at any time in case of PSA progression, symptomatic progressive disease, or change of antineoplastic therapy. The rationale for this schedule was to mimic a real-world setting where imaging is driven by clinical signs and symptoms or biochemical progression instead of a fixed pre-determined schedule every few months. Time intervals between imaging in ARASENS were varying as a result of this. **Response rate**: The draft scope mentions response rate as a relevant endpoint to be considered. ARASENS collected only PSA response rate as a secondary endpoint. As such, we suggest deleting the 'response rate' endpoint mentioned in the scope as it is not clear to what type of response it relates to.	Thank you for your comments. Progression-free survival and response rate are considered important outcomes for patients with late-stage cancer. Inclusion of these outcomes is also consistent with previous scopes in this disease area. "Response rate" may include measures of tumour, rather than biomarker, response. No changes made to scope.
	Tackle Prostate Cancer	Yes Adverse events are as important to patients as positive outocome. They look not only for *quantity* of life but *quality* also	Thank you for your comment. No action required.
	Prostate Cancer UK	We believe that the outcomes listed in the draft remit are appropriate and the measures will capture the health-related benefits and harms.	Thank you for your comment. No action required.

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Equality	Bayer	Bayer is not aware of any issues relating to inequalities.	Thank you for your comment. No action required.
	Tackle Prostate Cancer	See response above 'sub groups'	Thank you for your comment. Darolutamide will be appraised within its marketing authorisation. No action required.
	Prostate Cancer UK	We consider the draft remit to be sufficient with regards to the equality aims.	Thank you for your comment. No action required.
Other considerations	Bayer	No additional issues have been identified.	No action required.
	Tackle Prostate Cancer	No comments	No action required.
	Prostate Cancer UK	No comments	No action required.
Questions for consultation	Bayer	**Where do you consider darolutamide with androgen deprivation therapy and docetaxel will fit into the existing care pathway for hormone-sensitive metastatic prostate cancer?** Bayer anticipates darolutamide + docetaxel + ADT will be used as an additional treatment option for patients with metastatic hormone-sensitive prostate cancer who are suitable for chemotherapy treatment. It is anticipated	Thank you for your comments. No action required.

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		to displace to a considerable extent docetaxel with ADT as an alternative which significantly delays progression to hormone-relapsed disease, significantly prolongs survival, while maintaining the quality of life of patients. It could also be used as an alternative to enzalutamide + ADT in patients in which early treatment intensification for enhanced disease control is desirable, patients who are suitable for and willing to receive an early course of docetaxel ahead of a potential re-challenge with docetaxel in the metastatic hormone relapsed stage. Due to the favourable drug-on-drug interaction profile and toxicity profile of darolutamide, we also anticipate darolutamide + docetaxel + ADT to drive clinical decisions in situations where these considerations are clinically important, particularly after the initial 6 cycles of docetaxel at which point darolutamide would be the long-term main stay therapy. **Would degarelix be considered a comparator?** Bayer does not consider degarelix to be an appropriate comparator. It is used as an ADT in limited circumstances as an alternative to luteinising hormone-releasing hormone analogues (LHRHA) where there may be a risk of spinal cord compression due to the location of bone metastases. Darolutamide + docetaxel is intended to be used on top of background ADT. Therefore, degarelix is not a relevant comparator for this appraisal. This view is also backed up by clinical consensus. **Would darolutamide with androgen deprivation therapy and docetaxel be a candidate for managed access?** Darolutamide + docetaxel + ADT clearly demonstrates cost-effectiveness for routine commissioning. **Do you consider darolutamide with androgen deprivation therapy and docetaxel to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve**	

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		the way that current need is met (is this a 'step-change' in the management of the condition)? The new indication for darolutamide is already seen as being innovative by the MHRA who has granted an Innovation Passport and prioritised its licensing through accelerated approval. There continues to be a need for more efficacious treatment options for men with advanced prostate cancer and darolutamide + docetaxel + ADT has been demonstrated to significantly delay progression, improve survival, while maintaining the quality of life of patients compared to a long-established standard of care, thus representing a step-change in in management with significant improvements for patient prognosis. The need for such treatment options is even more apparent in the current post-COVID 19 context characterised by significant under referral and under treatment of prostate cancer patients, as highlighted by NHSE's in collaboration with PCUK 'Missing Men' campaign. The number of men being diagnosed with advanced prostate cancer is expected to only increase as more patients will be presenting to their clinicians. These men are in urgent need of an array of novel treatment approaches that aim to better control their disease through treatment intensification and that maximise their chances of survival. Bayer are keen to support this objective and build on the detection work by providing more treatment options. We expect this to be part of the Government's 10-year cancer plan and are keen to build on these ambitions. **Do you consider that the use of darolutamide with androgen deprivation therapy and docetaxel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** Darolutamide demonstrated a toxicity profile similar to placebo when added to docetaxel + ADT in ARASENS, whereas its distinct molecular structure has been shown to have limited drug-on-drug interactions (DDIs) when compared	

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		to other novel anti-hormonal agents. These interactions are important considerations in clinical practice and can have a substantial impact on efficacy 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 framework. Additionally, the psychological impact of delaying progression to mHRPC and the positive impact that this may have on patients may not be appropriately captured in the model and in the context of a randomised clinical trial. Clinical consensus has also indicated a potential distinct benefit of the darolutamide triple therapy in terms of tackling the PSA related anxiety of patients. A published systematic review highlights the important aspects and impact of PSA anxiety in patients with prostate cancer.[1] **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** 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.[2,3,4] It has also been shown to cause less frequent severe DDIs when compared to other	

[1] James, Callum, et al. "Fear of cancer recurrence and PSA anxiety in patients with prostate cancer: a systematic review." Supportive Care in Cancer (2022): 1-13.
[2] Floyd, Rebecca, et al. "Clinical relevance of drug–drug interactions with darolutamide." ONS 45th Annual Congress. ONS, 2020.
[3] Shore N, Zurth C, Fricke R, et al. Evaluation of Clinically Relevant Drug-Drug Interactions and Population Pharmacokinetics of Darolutamide in Patients with Nonmetastatic Castration-Resistant Prostate Cancer: Results of Pre-Specified and Post Hoc Analyses of the Phase III ARAMIS Trial. Target Oncol. 2019;14(5):527-539. doi:10.1007/s11523-019-00674-0
[4] Fizazi, Karim, et al. "Efficacy and safety outcomes of darolutamide in patients with nonmetastatic castration-resistant prostate cancer with comorbidities and concomitant medications from ARAMIS." (2022): 256-256.

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		novel anti-hormonal agents;[5] 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.[6] The British National Formulary (BNF) lists 30 potential interactions for darolutamide, considerably less than for other novel anti-hormonal agents used in prostate cancer: 201 for enzalutamide and 288 for apalutamide (accessed June 2022). Through the presentation of our cost-effectiveness analyses, Bayer will include all relevant benefits that can be expressed within the QALY calculations whilst being adherent to the NICE reference case. However, the clinical and economic impact of these interactions are difficult to quantify and include in a cost-effectiveness framework due to the general lack of data linking these interactions with hard clinical and cost outcomes.	
	Tackle Prostate Cancer	Where do you consider darolutamide with androgen deprivation therapy and docetaxel will fit into the existing care pathway for hormone-sensitive metastatic prostate cancer? *This is the first appraisal for 'triple concurrent therapy' for advanced prostate cancer. It combines drugs / drug groups that previously have been used as 'serial monotherapies' or 'dual therapy' of ADT with either docetaxel or a novel hormonal agent.* *The ability to have added therapy with apparently better outcomes and very few extra side effects may well be very acceptable to an appropriate group of patients.*	Thank you for your comments. No action required.

[5] Appukkuttan, S., et al. "PCN158 Potential Drug-Drug Interactions to Novel Anti-Androgen Therapies Among Non-Metastatic Castration-Resistant Prostate Cancer Patients." Value in Health 24 (2021): S49.
[6] Nubeqa (Darolutamide) Summary of Product Characteristics - https://www.medicines.org.uk/emc/product/11324

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		Would degarelix be considered a comparator? *Degarelix is not commonly used in UK except in specific clinical scenarios – e.g. where spinal cord compression problems may be imminent. An uncommonly used monotherapy would not seem to be a valid comparator on clinical grounds.* Would darolutamide with androgen deprivation therapy and docetaxel be a candidate for managed access? *Unable to comment on this aspect,* Do you consider darolutamide with androgen deprivation therapy and docetaxel to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? *Triple drug therapy as a first-line treatment for hormone sensitive metastatic PCa is certainly a innovative step in therapy. It could well be seen by patients as a logical step forward since many other cancers are treated with multiple therapies as a first-line approach.* Do you consider that the use of darolutamide with androgen deprivation therapy and docetaxel can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? *We are unable to make comment on this.* Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. *The only data I have been able to access is that provided to me by the pharmaceutical company manufacturing the drug under consideration.*	

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	Prostate Cancer UK	No comments	No action required.
Additional comments on the draft scope	Bayer	No comments	No action required.
	Tackle Prostate Cancer	No comments	No action required.
	Prostate Cancer UK	No comments	No action required.

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

Janssen
AstraZeneca