National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer [ID1359]

Response to consultee and commentator 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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Astellas Pharma Limited	No. We have suggested the following wording in line with the proposed indication of the submitted marketing authorisation: To appraise the clinical and cost effectiveness of enzalutamide within its marketing authorisation for treating adult men with non-metastatic castration-resistant prostate cancer.	Comments noted. In January 2013, NICE and the Department of Health and Social Care agreed that, following feedback received from stakeholders during scoping and appraisal consultations, the term 'castration-resistant prostate cancer' should be replaced with 'hormone-relapsed prostate cancer'. For equality reasons, the scope refers to adults

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			rather than adult 'men'. No action required.
Timing Issues	Astellas Pharma Limited	There is currently no medication licensed for treating non-metastatic castration-resistant prostate cancer.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Astellas Pharma Limited	Xtandi™ is trademarked. The data presented characterises the number of patients diagnosed with non-metastatic prostate cancer. The object of this remit – non-metastatic castration-resistant prostate cancer, is a further subset of the disease with fewer diagnosed men.	Comments noted. NICE does not use trademarks in its house style. No action required.
The technology/ intervention	Astellas Pharma Limited	The description of the technology is accurate.	Comment noted. No action required.
Population	Astellas Pharma Limited	The population to be evaluated is as follows: Adult men with non-metastatic castration-resistant prostate cancer. There are no groups within this population that should be considered separately.	Comment noted. No action required.
Comparators	Astellas Pharma Limited	ADT ADT + Bicalutamide There is currently no medicine licensed for the treatment of men with non-metastatic castration-resistant prostate cancer. ADT and ADT +	Comments noted. The background information has been amended to recognise that anti-androgens are included

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		Bicalutamide are alternative care (EAU Prostate Cancer Guidelines http://uroweb.org/guideline/prostate-cancer/ . Accessed on 14/03/18).	in androgen deprivation therapy.
Outcomes	Astellas Pharma Limited	The outcomes listed do not adequately capture the most important health related benefits of enzalutamide in the treatment population under consideration. Progression free survival is not an appropriate outcome measure for this indication. Outcome measures to be considered include: Metastasis Free Survival (MFS) Time to Prostate-Specific Antigen (PSA) Progression Overall Survival (OS) Time to next therapy for prostate cancer Time to treatment discontinuation Health-related quality of life measures measures Time to chemotherapy-free disease specific survival Time to chemotherapy-free survival Time to pain progression Safety PSA response rates	Comment noted. The scope does not include an exhaustive list of outcomes. The key outcome measures are considered to be: • Metastasis-free survival • Time to prostate-specific antigen progression • Overall survival • Adverse effects of treatment • Health-related quality of life. The scope has been amended to reflect these outcomes.
Economic analysis	Astellas Pharma Limited	A cost-utility analysis over a lifetime horizon to reflect the impact on survival of non-metastatic castration-resistant prostate cancer.	Comment noted. No action required.

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Equality and Diversity	Astellas Pharma Limited	There are no known equality issues.	Comment noted. No action required.
Innovation	Astellas Pharma Limited	There are currently no licensed products or consensus in guidelines on how to treat patients with non-metastatic castration-resistant prostate cancer, highlighting an unmet need for patients with this diagnosis. In men with non-metastatic castration-resistant prostate cancer baseline PSA levels and PSA velocity have been associated with time to first bone metastasis and overall survival. (Mathew R. Smith et al. Disease and Host characteristics as predictors of time to first Bone Metastasis and Death in Men with Progressive Castration-Resistant Nonmetastatic Prostate cancer. Cancer. 2011 May 15; 117 (10); Mathew R. Smith et al. Natural History of Rising Serum Prostate-Specific Antigen in Men with Castrate Nonmetastatic Prostate Cancer. Journal of Clinical Oncology. 2005 May Vol 23; No.13).The development of metastases has been shown to have an impact on a patients' prognosis with 5-year survival dropping from 100% with localized disease to 30% on development of distant metastases. (https://seer.cancer.gov/archive/csr/1975_2009_pops09/results_merged/topic_survival.pdf.Accessed on 14/03/18). The development of distant metastases can also significantly affect quality of life as a consequence of the associated effects including pain and risk of skeletal related events e.g. pathological fractures, spinal cord compression. There is a need for a licensed treatment option that can slow/prevent disease progression and delay the development of metastases and the associated complications and decline in health in patients with non-metastatic castration-resistant prostate cancer.	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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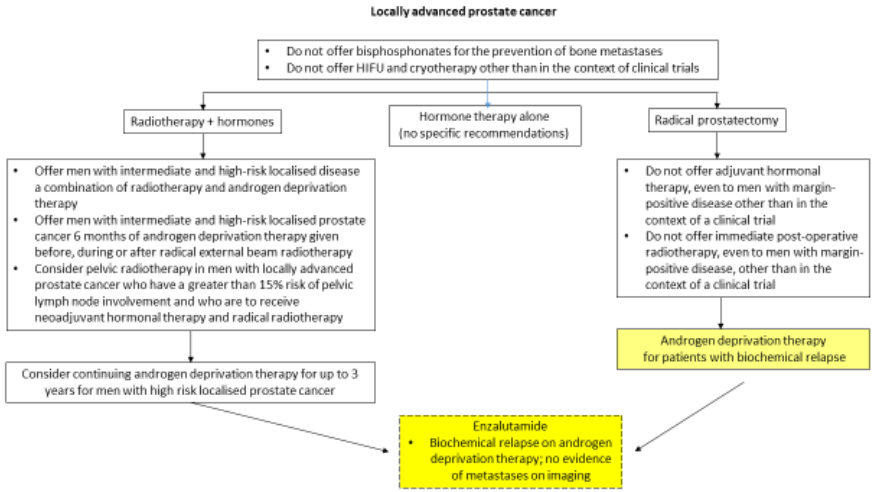
Questions for consultation	Astellas Pharma Limited	Questions for consultation not previously addressed: • Where do you consider enzalutamide will fit into the existing NICE pathway, 'Prostate cancer'? Our proposal for enzalutamide's place in the NICE pathway for locally advanced prostate cancer is shown below. We have also identified that androgen deprivation therapy for patients with biochemical relapse is a relevant step for the pathway (highlighted in yellow boxes).  	Comments noted. No action required.

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		• Do you consider that the use of enzalutamide can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No. • To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No. Enzalutamide is already licensed and reimbursed for its existing indications in metastatic castration resistant prostate cancer. • NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). The STA process is appropriate for this topic.	
Additional comments on the draft scope	Astellas Pharma Limited	Please note the letter of Dr Andreas Karas of 13th March 2018 in relation to the scoping workshop.	Comment noted. Although scoping workshops are held for some topics, they are

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			not a compulsory element of the scoping process. A scoping workshop was not considered necessary for this topic because NICE has extensive experience on previous prostate cancer appraisals and clinical guidelines in this disease area.
	Clinical expert contacted by NICE	**Q:** Do such patients continue to receive hormone therapy (this includes androgen deprivation therapy with or without anti-androgens) despite being castration-resistant/hormone-relapsed? **A:** Yes the androgen deprivation therapy is continued on a regular basis. Anti-androgens like Bicalutamide may be used in conjunction and are only continued if responding otherwise stopped though androgen deprivation therapy is continued. **Q:** Are radical surgery or radical radiotherapy (with or without hormonal therapy) used in these patients? **A:** If there is evidence of oligometastatic disease on restaging then possible to use these options....more commonly it is stereotactic radiotherapy. Overall this is in a small proportion of cases. **Q:** Is active surveillance a treatment option? **A:** These patients are on ADT so technically it is not active surveillance but if the question refers to not doing anything other than continuing ADT till	Comments noted. The background and comparators sections of the scope have been updated to reflect this information.

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		there is evidence of metastatic disease then answer is yes that is an option but more so because there are no proven and licensed and reimbursed options in this setting.	
	Clinical expert contacted by NICE	Castrate resistant prostate cancer is a disease state defined by rising PSA levels, despite a serum testosterone level of <50ng/dl (achieved by androgen deprivation therapy or orchidectomy). Prior to reaching this disease state, most men will have received definitive treatment at the time of diagnosis, either with radical surgery or radical radiotherapy, with or without a course of hormone therapy. If after this treatment the PSA rises (biochemical recurrence), most patients are started on androgen deprivation therapy, with LHRH analogue therapy (i.e. goserelin). Whilst on this therapy and the PSA level rises (castrate resistance), an anti-androgen (i.e. bicalutamide) is introduced (combined androgen blockade). Once the PSA rises on this regimen, the anti-androgen is stopped, but patients continue indefinitely on LHRH analogue therapy. If there is no radiological evidence of metastatic disease, with a rising PSA, then patients in our practice are started on low dose dexamethasone (0.5mg daily). Once a patient's PSA progresses on dexamethasone, there are currently no available treatment options outside of clinical trials until metastatic disease is seen on imaging. There was a UK wide survey published in abstract form in 2016 on the management of non-metastatic castrate resistant prostate cancer (Latif et al . JCO 2016: 34(15 suppl e16520), where 96 oncologists responded	Comments noted. The background and comparators sections of the scope have been updated to reflect this information.

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		regarding the management options for a 65 year old man developing non metastatic castrate resistant prostate cancer 2 years after radical radiotherapy. Management options considered included dexamethasone, 2nd generation hormone therapy (via clinical trials) and active monitoring (monitoring the absolute PSA value and the PSA doubling time as important treatment decision making factors). **Q:** Do such patients continue to receive hormone therapy (this includes androgen deprivation therapy with or without anti-androgens) despite being castration-resistant/hormone-relapsed? **A:** The non-metastatic castrate-resistant patients continue indefinitely on androgen deprivation therapy unless they have had an orchidectomy. **Q:** Are radical surgery or radical radiotherapy (with or without hormonal therapy) used in these patients? **A:** No, patients would have already had this primary radical treatment prior to developing non-metastatic castration resistant prostate cancer. Some patients may be considered for salvage treatment (with surgery or radiotherapy) on initial PSA progression, with non-castrate testosterone levels, but not once you have castrate resistant prostate cancer. **Q:** Is active surveillance a treatment option? **A:** No, active surveillance is for patients who have low risk prostate cancer, who have not yet had definitive treatment for their prostate cancer and are surveyed to determine the right time for treatment dependent on PSA kinetics, prostate imaging, histological and clinical factors.	

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	Clinical expert contacted by NICE	The term “non-metastatic castration-resistant/hormone-relapsed prostate cancer” means that patients have either - Been diagnosed localised prostate cancer and have undergone a radical local treatment (can be surveillance followed by surgery or radiotherapy or RT/S upfront). If subsequently PSA raises without metastatic disease on imaging they are diagnosed non-metastatic prostate cancer. This than is typically treated with long-term LHRH injections (reducing male hormone (androgen or testosterone) levels); an alternative is oral bicalutamide (drug inhibiting the action of androgens). If the PSA increases again some patients respond to a switch to MAB (LHRH and bicalutamide); if there is a response sometimes bicalutamide withdrawal can again reduce the PSA. In the situation of raising PSA without metastatic disease, current standard care is continuing LHRH injections and monitoring of the PSA plus regular imaging. Apalutamide or Enzalutamide with continuing LHRH therapy have been used in the trial setting and were (correctly) compared to LHRH therapy only. If there is evidence of metastatic progression other therapies in addition to LHRH therapies are indicated (chemotherapy, abiraterone or enzalutamide as per NICE guidance) - Been diagnosed localised prostate cancer and have not undergone a radical local treatment because of comorbidity, fitness or patient choice and are treated with primary ADT or primary ADT and Radiotherapy. Primary ADT is hormone therapy only (LHRH, orchidectomy or bicalutamide) without radical local treatments; normally used for patients with a life expectancy <5 years. If the PSA increases again some patients respond to a switch to MAB (LHRH and bicalutamide); if there is a response sometimes bicalutamide withdrawal can again reduce the PSA; sometimes Stilboestrol or palliative radiotherapy to the local disease is useful.	Comments noted. The background and comparators sections of the scope have been updated to reflect this information.

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		Q: Do such patients continue to receive hormone therapy despite being castration-resistant/hormone-relapsed? **A:** Patients are always continued on hormone therapy as stopping it will increase the testosterone, the PSA doubling time and ultimately the time to metastatic disease. The fact that some cancer cells do not respond anymore completely to testosterone withdrawal does not mean it has no effect at all. **Q:** Are radical surgery or radical radiotherapy (with or without hormonal therapy) used in these patients? **A:** As above, these treatments are used at initial diagnosis without metastatic disease in the primary hormone sensitive setting. **Q:** Is active surveillance a treatment option? **A:** No, active surveillance is used at initial diagnosis without metastatic disease in the primary hormone sensitive setting.	

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

Tackle Prostate Cancer
Department of Health and Social Care