NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Astellas

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Alison Tree, clinical expert nominated by

4. **Evidence Review Group critique of company response** – prepared by the Aberdeen HTA Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Enzalutamide for treating non-metastatic hormone-relapsed prostate cancer

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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 number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Astellas	**Section 3.8** – The overall survival data are immature so there is no evidence that enzalutamide confers an overall survival benefit relative to placebo PROSPER was only powered for its primary endpoint metastasis-free survival (MFS). Overall survival (OS) results reported to date are aligned with scientific expectations and already show a trend towards a survival benefit. Disease-specific mortality is negligible in patients with localised prostate cancer. In solid tumours, it is the metastases interfering with the functioning of vital organs and/or draining energy from the body that may ultimately lead to cancer-related death. As long as prostate cancer has not yet metastasised, patients are thus not expected to die from their cancer (section 3.14 of the ACD). Because they represent an elderly population, patients with high-risk non-metastatic hormone-relapsed prostate cancer (nmHRPC) may actually die from natural causes or unrelated comorbidities before their cancer becomes fatal. At this stage of the PROSPER trial, it is therefore challenging to already demonstrate a statistically significant OS benefit in this population. Nevertheless, we believe that there is a clear and strong scientific rationale why the delay of metastasis produced by enzalutamide can only have a positive impact on patients' quality of life and the risk of cancer-related death. Moreover, both the androgen receptors inhibitors enzalutamide and apalutamide have shown a very similar trend towards OS gains in the PROSPER and SPARTAN studies, which were of similar design in comparable patient groups. A meta-analysis of pooled data from these two studies has shown a statistically significant OS benefit (Bhindi and Karnes 2018). This supports the view that there have not yet been enough OS events in the individual studies to demonstrate a statistically significant survival benefit. Citation for the manuscript is: Bhindi B, Karnes RJ. Novel Nonsteroidal Antiandrogens and Overall Survival in Nonmetastatic Castration-resistant Prostate Cancer. Eur Urol. 2018 Oct;74(4):534-535. doi: 10.1016/j.eururo.2018.05.021	Comment noted. The committee considered the overall survival data to be immature key to populating the economic model (Final Appraisal Determination Section 3.8)
2	Consultee (company)	Astellas	**Section 3.9** – The committee concluded that enzalutamide may be less effective with respect to overall survival when used earlier in the treatment pathway, both absolutely and relatively. In the New England Journal of Medicine editorial accompanying the main publication of the PROSPER results, Harvard Medical School professor Matthew R. Smith shared an opposing viewpoint, by stating: • "Although the SPARTAN and PROSPER trials were not designed to evaluate sequential treatment formally, these two trials provide valuable evidence about early versus later therapy. The majority of the	Comment noted. The committee considered evidence from the PROPSER trial to be most appropriate. The

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			patients in the placebo group in each trial subsequently received approved therapy for metastatic disease. Despite the high rates of subsequent therapy, both trials showed improvements in all secondary end points, including late clinical events that followed radiographic progression by many months. In the SPARTAN trial, for example, apalutamide was associated with prolongation in the time to symptomatic progression and in the time to the initiation of cytotoxic chemotherapy. Apalutamide and enzalutamide were also each associated with longer overall survival, although longer follow-up is required in order to evaluate their effects on mortality reliably." • "… the FDA approval of apalutamide for non-metastatic prostate cancer and the anticipated approval of enzalutamide in the same context represent important steps forward for men with rising PSA levels during androgen deprivation therapy. The benefit–risk evaluation suggests that treatment with either drug is better than waiting until the appearance of metastases." Citation for the related editorial is: Smith MR. Progress in Nonmetastatic Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2531-2532. doi: 10.1056/NEJMe1805733.	committee did not change its conclusion about relative and absolute effect of enzalutamide (Final Appraisal Determination Section 3.10)
3	Consultee (company)	Astellas	**Section 3.10** – The committee agreed that the use of subsequent therapies in PROSPER introduced bias... The committee concluded that the company should have adjusted for the effect of the subsequent treatments not available in the NHS and for which there is evidence of a survival benefit. As it is generally considered that there is insufficient evidence to conclude that the sequential use of enzalutamide and abiraterone would have additional survival benefits (TA316) and only a small minority of PROSPER patients have followed a treatment sequence that would be unavailable in the NHS, Astellas believes it is unlikely that any outcomes have been significantly biased. In the context of a double-blind randomised controlled trial (RCT), the PROSPER protocol indeed allowed physicians to treat their metastatic patients with active therapies licensed in the metastatic HRPC (mHRPC) setting. The proportion of PROSPER patients in the enzalutamide arm having received a treatment sequence that would be unavailable in NHS clinical practice (i.e. either enzalutamide or abiraterone after blinded enzalutamide) as a result of this, however, was limited to <7% of subjects at the time of the first interim analysis of OS (IA1). Therefore, we believe that it is unlikely that subsequent treatments had a meaningful impact on the OS outcome. The use of enzalutamide or abiraterone after ADT (upon development of metastases in the placebo arm) would be allowed in NHS clinical practice and their treatment effects should thus not be adjusted for.	Comment noted. The committee acknowledged this as an uncertainty and the difficulty of adjusting for this. (Final Appraisal Determination Section 3.11)
4	Consultee (company)	Astellas	**Section 3.11** – The committee concluded that there was not enough evidence from PROSPER to show that enzalutamide improved quality of life compared with placebo after 22 months' follow-up Patients with non-metastatic prostate cancer are generally asymptomatic and have good quality of life. Symptoms increase when metastases develop. By prolonging the period before metastases develop, enzalutamide aims to delay deterioration of, rather than improve, these patients' quality of life. This is indeed what was observed in PROSPER. Although enzalutamide was used as an add-on to ADT, it did not have a	Comment noted. The committee noted this point but concluded that this benefit was not reflected in the economic

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			negative impact on overall quality of life and it significantly delayed time to deterioration of several subscales of the patient-reported outcome questionnaires collected in PROSPER (e.g., FACT-P emotional wellbeing, prostate cancer scale and total score, and EORTC QLQ-PR25 urinary and bowel symptoms) compared with placebo.	model (Final Appraisal Determination Section 3.12)
5	Consultee (company)	Astellas	**Section 3.13** – The model structure chosen by the company meant that the company had to break down the already uncertain outcome of overall survival into death... [the committee] further considered that the company should have at least validated the output of its model against the standard 3-state partitioned survival model... The committee concluded that the model structure chosen by the company introduced additional uncertainty to the model estimates. **Section 3.16** – Survival in each progressed state is likely to differ We are still of the opinion that the model structure and semi-Markov approach represent the best methods to inform the current decision problem, for the following reasons: • Whilst we agree that the standard 3-state partitioned survival (PartSA) model is used very commonly in (late stage) oncology indications, it is not particularly useful in early-stage disease. For example, a Markov approach can capture the progressive nature of metastatic disease very well (i.e. gradually decreasing utility values in successive health states) and provides much more flexibility to model downstream treatments than a PartSA model could. • NICE guidance on enzalutamide for the pre-chemo mHRPC setting (TA377) states, "The ERG commented that in the model, a patient's probability of dying at a particular time point was the same regardless of their health state. The ERG considered this to be implausible because it meant that people with stable, asymptomatic or mildly symptomatic disease on their first treatment had the same risk of dying as people with progressive disease on palliative care after up to 3 lines of active treatment had failed". The same rationale applies even more to the risks of dying between non-metastatic vs. metastatic patients in the current setting. Moreover, in section 3.16 of the current ACD, the committee criticises that "all patients with metastatic disease in the model had the same rate of death before, during and after docetaxel for metastatic disease". Whereas a Markov approach allows the user to explore scenarios with varying rates of death in the different health states, a PartSA approach does not. • The Markov and PartSA approaches are merely modelling techniques that divide the model population over the different health states. Starting from identical clinical data (e.g. survival curves in this case), PartSA and Markov models are expected to produce similar results, if modelling and fitting have been done appropriately (NICE DSU TSD19). In our model, all curves were extrapolated and fitted in accordance to NICE DSU TSD14. The results of the 'single OS curve' scenario #7 included in our submission is therefore expected to produce similar results to a PartSA model.	Comment noted. The committee did not change its conclusions about the model structure (Final Appraisal Determination Section 3.14)
6	Consultee (company)	Astellas	**Section 3.16** – It is more appropriate to use metastasis-free survival rather than time to stopping treatment with the second interim analysis	Comment noted. The committee

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			Section 3.17 – It is more appropriate to use data for overall survival from the second rather than the first interim analysis Taken individually, both of the above-mentioned opinions seem logical. It is, however, important to realise that survival endpoints (e.g. MFS and OS) are not structurally independent and that there are a number of dependencies between these measures (NICE DSU TSD19). For example, any pre-progression death contributes to both the MFS and OS endpoint, death cannot be followed by metastasis... etc. Therefore, mixing data from different data cuts (e.g. MFS from IA1 and OS from IA2) introduces structural and methodological problems to the economic analysis that likely outweigh any benefit of using slightly more mature OS data. This view was supported by independent expert advice we obtained before submission (reference #72 of Document B). Moreover, the ERG raised similar concerns and were hesitant to combine MFS data with survival data from IA2 (section 5.3.2 and 5.4 of the ERG report). Therefore, we believe that it was appropriate to combine MFS and IA1 OS data in our base case analysis, with an exploratory scenario combining time to treatment discontinuation (TTD) and OS data from IA2 in our submission.	acknowledged the lack of available data to populate the model but did not change its conclusions about the most appropriate analysis (Final Appraisal Determination Sections 3.18 and 3.19)
7	Consultee (company)	Astellas	**Section 3.19 -** The committee concluded that there was a disconnection between observed and modelled overall survival in both the company's and ERG's model All parametric survival functions used in our model were constructed on the basis of, and fitted to, PROSPER patient-level data for the within-trial period and extrapolated beyond the trial observation period, as per NICE DSU TSD14 and good practice guidelines on survival analysis. The median OS in the model's base-case analysis for the ADT group was estimated around 48 months, which is consistent with historic median OS data observed in the placebo control arms of clinical studies in similar populations reported by Nelson et al (46.1 months) and Smith et al (44.8 months). It has been shown that the pre-metastasis death rates are not driving the model's outputs, which is consistent with the fact that non-metastatic patients are unlikely to die from prostate cancer. With regard to post progression survival data, the ERG mentioned that "it is reassuring to note that extrapolation... has been externally validated against OS data from the PREVAIL trial". Together with the arguments we already presented in comment #1 of this table, these elements strengthen our belief that the estimates produced by our model are realistic and clinically plausible. References: - Nelson JB, Love W, Chin JL, Saad F, Schulman CC, Sleep DJ, Qian J, Steinberg J, Carducci M; Atrasentan Phase 3 Study Group. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer. 2008 Nov 1;113(9):2478-87. doi: 10.1002/cncr.23864. - Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K, Van Veldhuizen P, Morote J, Ye Z, Dansey R, Goessl C. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol. 2013 Oct 20;31(30):3800-6. doi: 10.1200/JCO.2012.44.6716.	Comments noted. The committee did not change its conclusions about the disconnection between observed and modelled overall survival. (Final Appraisal Determination Section 3.20)

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8	Consultee (company)	Astellas	**Section 3.26** - Enzalutamide plus ADT is not cost effective compared with ADT alone. The ERG presented a base-case ICER of £56,168 per QALY gained We have several concerns about the information presented in this section of the ACD, including: • As explained in comment #6, combining MFS from IA1 with OS data from IA2 in the economic analysis is methodologically problematic because these two endpoints are structurally dependent. The ERG has recognised that such an approach is inconsistent (ERG report section 5.3.2) and has stated that "The ERG preferred set of assumptions are incorporated in scenario #7" (ERG report section 5.3.2 and Table 33). ERG scenario #7 indeed combines MFS data with OS data from IA1 and results in an ICER of £35,628 per QALY gained. Nevertheless, the committee has presented ERG scenario #9, combining MFS with IA2 OS data and resulting in an ICER of £56,168 as "the base case ICER presented by the ERG" (ACD section 3.26) • Both ERG scenarios #7 and #9 use a utility value of 0.844 previously obtained from the PREVAIL study (section 5.2.7 and table 33 of the ERG report and TA377), although the committee considers the utility value derived from PROSPER to be more appropriate because it used the same source of clinical data (ACD section 3.23) • An economic analysis combining the ERG preferred assumptions #2, #4 and #7 (equalised monitoring and testing frequencies, MACE costs increased to £3,279, and median duration in PD1 following progression on enzalutamide of 3.8 months) with the committee preferred utility value for the PD1 health state, and IA2 data for TTD, pre- and postTD survival, results in an ICER of £27,800 per QALY gained and suggests that enzalutamide could be considered both clinically beneficial and cost-effective in this setting.	Comments noted. The committee did not change its preferred cost-effectiveness ICER. (Final Appraisal Determination Section 3.27)
1	Consultee (professional group)	NCRI Prostate CSG	Section 3.3 I don't think this statement is correct: "The committee heard that docetaxel is also offered to some people in this setting, but understood that this was not supported by NHS England " I think this comment relates to the use of docetaxel for upfront (newly diagnosed) metastatic prostate cancer. I don't believe anyone is using docetaxel in the setting being discussed in this document i.e. in non-metastatic disesae.	Comment noted. The Final Appraisal Determination has been amended to reflect this.
2	Consultee (professional group)	NCRI Prostate CSG	Section 3.8 This statement is complex and may need some explaining, or else removing "However, it heard from the clinical experts that patients who get enzalutamide later rather than earlier do not	Comment noted. The Final Appraisal Determination

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			appear to catch up “ I think what we were saying here is explained in the next section (3.9) with regard to the hazard ratios in various scenarios i.e. that the absolute benefit of enzalutamide appears to be more, not less, if the drug is given later.	has been further explained in Section 3.9 to question the survival benefit of active therapies in the placebo arm.
3	Consultee (professional group)	NCRI Prostate CSG	Section 3.9 “The clinical experts state that, for hormone-sensitive prostate cancer, there was some evidence to suggest that the earlier enzalutamide is used, the greater the survival benefit. “ I don't recall saying that the benefit of enzalutamide was greater if used earlier in the pathway and I don't know of any evidence that suggests that is true for this particular drug. There is such evidence for Abiraterone and Docetaxel, so we may have said that for other similar drugs, earlier appears to be better.	Comment noted. The Final Appraisal Determination has been amended. Section 3.10
4	Consultee (professional group)	NCRI Prostate CSG	Section 3.20 I would say that more than 40% of patients post-diagnosis of metastatic disease receive docetaxel at some point, although this would probably affect both arms equally (caveat: it is possible that patients receiving Enza in this setting would therefore get docetaxel earlier – I don't think this was modelled by the company and would not be to their favour in terms of the economic model).	Comment noted. The Final Appraisal Determination has been amended. Section 3.21

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on 7 February 2019 **email:** TACommB@nice.org.uk / NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Astellas Pharma Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Please submit using NICE Docs

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	even more to the risks of dying between non-metastatic vs. metastatic patients in the current setting. Moreover, in section 3.16 of the current ACD, the committee criticises that "all patients with metastatic disease in the model had the same rate of death before, during and after docetaxel for metastatic disease". Whereas a Markov approach allows the user to explore scenarios with varying rates of death in the different health states, a PartSA approach does not. • The Markov and PartSA approaches are merely modelling techniques that divide the model population over the different health states. Starting from identical clinical data (e.g. survival curves in this case), PartSA and Markov models are expected to produce similar results, if modelling and fitting have been done appropriately (NICE DSU TSD19). In our model, all curves were extrapolated and fitted in accordance to NICE DSU TSD14. The results of the 'single OS curve' scenario #7 included in our submission is therefore expected to produce similar results to a PartSA model.
6	**Section 3.16** – It is more appropriate to use metastasis-free survival rather than time to stopping treatment with the second interim analysis **Section 3.17** – It is more appropriate to use data for overall survival from the second rather than the first interim analysis Taken individually, both of the above-mentioned opinions seem logical. It is, however, important to realise that survival endpoints (e.g. MFS and OS) are not structurally independent and that there are a number of dependencies between these measures (NICE DSU TSD19). For example, any pre-progression death contributes to both the MFS and OS endpoint, death cannot be followed by metastasis... etc. Therefore, mixing data from different data cuts (e.g. MFS from IA1 and OS from IA2) introduces structural and methodological problems to the economic analysis that likely outweigh any benefit of using slightly more mature OS data. This view was supported by independent expert advice we obtained before submission (reference #72 of Document B). Moreover, the ERG raised similar concerns and were hesitant to combine MFS data with survival data from IA2 (section 5.3.2 and 5.4 of the ERG report). Therefore, we believe that it was appropriate to combine MFS and IA1 OS data in our base case analysis, with an exploratory scenario combining time to treatment discontinuation (TTD) and OS data from IA2 in our submission.
7	**Section 3.19 -** The committee concluded that there was a disconnection between observed and modelled overall survival in both the company's and ERG's model All parametric survival functions used in our model were constructed on the basis of, and fitted to, PROSPER patient-level data for the within-trial period and extrapolated beyond the trial observation period, as per NICE DSU TSD14 and good practice guidelines on survival analysis. The median OS in the model's base-case analysis for the ADT group was estimated around 48 months, which is consistent with historic median OS data observed in the placebo control arms of clinical studies in similar populations reported by Nelson et al (46.1 months) and Smith et al (44.8 months). It has been shown that the pre-metastasis death rates are not driving the model's outputs, which is consistent with the fact that non-metastatic patients are unlikely to die from prostate cancer. With regard to post progression survival data, the ERG mentioned that "it is reassuring to note that extrapolation... has been externally validated against OS data from the PREVAIL trial". Together with the arguments we already presented in comment #1 of this table, these elements strengthen our belief that the estimates produced by our model are realistic and clinically plausible. References: - Nelson JB, Love W, Chin JL, Saad F, Schulman CC, Sleep DJ, Qian J, Steinberg J, Carducci M; Atrasentan Phase 3 Study Group. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer. 2008 Nov 1;113(9):2478-87. doi: 10.1002/cncr.23864. - Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K,

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	Van Veldhuizen P, Morote J, Ye Z, Dansey R, Goessl C. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol. 2013 Oct 20;31(30):3800-6. doi: 10.1200/JCO.2012.44.6716.
8	**Section 3.26** - Enzalutamide plus ADT is not cost effective compared with ADT alone. The ERG presented a base-case ICER of £56,168 per QALY gained We have several concerns about the information presented in this section of the ACD, including: • As explained in comment #6, combining MFS from IA1 with OS data from IA2 in the economic analysis is methodologically problematic because these two endpoints are structurally dependent. The ERG has recognised that such an approach is inconsistent (ERG report section 5.3.2) and has stated that "The ERG preferred set of assumptions are incorporated in scenario #7" (ERG report section 5.3.2 and Table 33). ERG scenario #7 indeed combines MFS data with OS data from IA1 and results in an ICER of £35,628 per QALY gained. Nevertheless, the committee has presented ERG scenario #9, combining MFS with IA2 OS data and resulting in an ICER of £56,168 as "the base case ICER presented by the ERG" (ACD section 3.26) • Both ERG scenarios #7 and #9 use a utility value of 0.844 previously obtained from the PREVAIL study (section 5.2.7 and table 33 of the ERG report and TA377), although the committee considers the utility value derived from PROSPER to be more appropriate because it used the same source of clinical data (ACD section 3.23) • An economic analysis combining the ERG preferred assumptions #2, #4 and #7 (equalised monitoring and testing frequencies, MACE costs increased to £3,279, and median duration in PD1 following progression on enzalutamide of 3.8 months) with the committee preferred utility value for the PD1 health state, and IA2 data for TTD, pre- and postTD survival, results in an ICER of £27,800 per QALY gained and suggests that enzalutamide could be considered both clinically beneficial and cost-effective in this setting.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Dr Alison Tree, representative of the NCRI Prostate CSG
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No links to the tobacco industry
Name of commentator person completing form:	[**Dr Alison Tree**

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Section 3.3 I don't think this statement is correct: "The committee heard that docetaxel is also offered to some people in this setting, but understood that this was not supported by NHS England " I think this comment relates to the use of docetaxel for upfront (newly diagnosed) metastatic prostate cancer. I don't believe anyone is using docetaxel in the setting being discussed in this document i.e. in non-metastatic disesae.
2	Section 3.8 This statement is complex and may need some explaining, or else removing "However, it heard from the clinical experts that patients who get enzalutamide later rather than earlier do not appear to catch up " I think what we were saying here is explained in the next section (3.9) with regard to the hazard ratios in various scenarios i.e. that the absolute benefit of enzalutamide appears to be more, not less, if the drug is given later.
3	Section 3.9 "The clinical experts state that, for hormone-sensitive prostate cancer, there was some evidence to suggest that the earlier enzalutamide is used, the greater the survival benefit. " I don't recall saying that the benefit of enzalutamide was greater if used earlier in the pathway and I don't know of any evidence that suggests that is true for this particular drug. There is such evidence for Abiraterone and Docetaxel, so we may have said that for other similar drugs, earlier appears to be better.
4	Section 3.20 I would say that more than 40% of patients post-diagnosis of metastatic disease receive docetaxel at some point, although this would probably affect both arms equally (caveat: it is possible that patients receiving Enza in this setting would therefore get docetaxel earlier – I don't think this was modelled by the company and would not be to their favour in terms of the economic model).
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Astellas Pharma Ltd	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A	
Name of commentator person completing form:	[redacted]	

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1	**Section 3.8** – The overall survival data are immature so there is no evidence that enzalutamide confers an overall survival benefit relative to placebo PROSPER was only powered for its primary endpoint metastasis-free survival (MFS). Overall survival (OS) results reported to date are aligned with scientific expectations and already show a trend towards a survival benefit. Disease-specific mortality is negligible in patients with localised prostate cancer. In solid tumours, it is the metastases interfering with the functioning of vital organs and/or draining energy from the body that may ultimately lead to cancer-related death. As long as prostate cancer has not yet metastasised, patients are thus not expected to die from their cancer (section 3.14 of the ACD). Because they represent an elderly population, patients with high-risk non-metastatic hormone-relapsed prostate cancer (nmHRPC) may actually die from natural causes or unrelated comorbidities before their cancer becomes fatal. At this stage of the PROSPER trial, it is therefore challenging to already demonstrate a statistically significant OS benefit in this population. Nevertheless, we believe that there is a clear and strong scientific rationale why the delay of metastasis produced by enzalutamide can only have a positive impact on patients' quality of life and the risk of cancer-related death. Moreover, both the androgen receptors inhibitors enzalutamide and apalutamide have shown a very similar trend towards OS gains in the PROSPER and SPARTAN studies, which were of similar design in comparable patient groups. A meta-analysis of pooled data from these two studies has shown a statistically significant OS benefit (Bhindi and Karnes 2018). This supports the view that there have not yet been enough OS events in the individual studies to demonstrate a statistically significant survival benefit. Citation for the manuscript is: Bhindi B, Karnes RJ. Novel Nonsteroidal Antiandrogens and Overall Survival in Nonmetastatic Castration-resistant Prostate Cancer. Eur Urol. 2018 Oct;74(4):534-535. doi: 10.1016/j.eururo.2018.05.021	

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2	**Section 3.9** – The committee concluded that enzalutamide may be less effective with respect to overall survival when used earlier in the treatment pathway, both absolutely and relatively. In the New England Journal of Medicine editorial accompanying the main publication of the PROSPER results, Harvard Medical School professor Matthew R. Smith shared an opposing viewpoint, by stating: • "Although the SPARTAN and PROSPER trials were not designed to evaluate sequential treatment formally, these two trials provide valuable evidence about early versus later therapy. The majority of the patients in the placebo group in each trial subsequently received approved therapy for metastatic disease. Despite the high rates of subsequent therapy, both trials showed improvements in all secondary end points, including late clinical events that followed radiographic progression by many months. In the SPARTAN trial, for example, apalutamide was associated with prolongation in the time to symptomatic progression and in the time to the initiation of cytotoxic chemotherapy. Apalutamide and enzalutamide were also each associated with longer overall survival, although longer follow-up is required in order to evaluate their effects on mortality reliably." • "… the FDA approval of apalutamide for non-metastatic prostate cancer and the anticipated approval of enzalutamide in the same context represent important steps forward for men with rising PSA levels during androgen deprivation therapy. The benefit–risk evaluation suggests that treatment with either drug is better than waiting until the appearance of metastases." Citation for the related editorial is: Smith MR. Progress in Nonmetastatic Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2531-2532. doi: 10.1056/NEJMe1805733.	
3	**Section 3.10** – The committee agreed that the use of subsequent therapies in PROSPER introduced bias... The committee concluded that the company should have adjusted for the effect of the subsequent treatments not available in the NHS and for which there is evidence of a survival benefit. As it is generally considered that there is insufficient evidence to conclude that the sequential use of enzalutamide and abiraterone would have additional survival benefits (TA316) and only a small minority of PROSPER patients have followed a treatment sequence that would be unavailable in the NHS, Astellas believes it is unlikely that any outcomes have been significantly biased. In the context of a double-blind randomised controlled trial (RCT), the PROSPER protocol indeed allowed physicians to treat their metastatic patients with active therapies licensed in the metastatic HRPC (mHRPC) setting.	

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	The proportion of PROSPER patients in the enzalutamide arm having received a treatment sequence that would be unavailable in NHS clinical practice (i.e. either enzalutamide or abiraterone after blinded enzalutamide) as a result of this, however, was limited to <7% of subjects at the time of the first interim analysis of OS (IA1). Therefore, we believe that it is unlikely that subsequent treatments had a meaningful impact on the OS outcome. The use of enzalutamide or abiraterone after ADT (upon development of metastases in the placebo arm) would be allowed in NHS clinical practice and their treatment effects should thus not be adjusted for.	
4	**Section 3.11** – The committee concluded that there was not enough evidence from PROSPER to show that enzalutamide improved quality of life compared with placebo after 22 months' follow-up Patients with non-metastatic prostate cancer are generally asymptomatic and have good quality of life. Symptoms increase when metastases develop. By prolonging the period before metastases develop, enzalutamide aims to delay deterioration of, rather than improve, these patients' quality of life. This is indeed what was observed in PROSPER. Although enzalutamide was used as an add-on to ADT, it did not have a negative impact on overall quality of life and it significantly delayed time to deterioration of several subscales of the patient-reported outcome questionnaires collected in PROSPER (e.g., FACT-P emotional wellbeing, prostate cancer scale and total score, and EORTC QLQ-PR25 urinary and bowel symptoms) compared with placebo.	
5	**Section 3.13** – The model structure chosen by the company meant that the company had to break down the already uncertain outcome of overall survival into death... [the committee] further considered that the company should have at least validated the output of its model against the standard 3-state partitioned survival model... The committee concluded that the model structure chosen by the company introduced additional uncertainty to the model estimates. **Section 3.16** – Survival in each progressed state is likely to differ We are still of the opinion that the model structure and semi-Markov approach represent the best methods to inform the current decision problem, for the following reasons: • Whilst we agree that the standard 3-state partitioned survival (PartSA) model is used very commonly in (late stage) oncology indications, it is not particularly useful in early-stage disease. For example, a Markov approach can capture the progressive nature of metastatic disease very	With respect to the company's point that "The results of the 'single OS curve' scenario #7 included in our submission is therefore expected to produce similar results to a PartSA model." This is likely true but the ERG note that this scenario remains problematic since is still uses the less mature OS data from IA1, which results in sizable extrapolated OS benefit in favour of early enzalutamide treatment which does not appear consistent with the observed OS data at IA2.

	well (i.e. gradually decreasing utility values in successive health states) and provides much more flexibility to model downstream treatments than a PartSA model could. • NICE guidance on enzalutamide for the pre-chemo mHRPC setting (TA377) states, "The ERG commented that in the model, a patient's probability of dying at a particular time point was the same regardless of their health state. The ERG considered this to be implausible because it meant that people with stable, asymptomatic or mildly symptomatic disease on their first treatment had the same risk of dying as people with progressive disease on palliative care after up to 3 lines of active treatment had failed". The same rationale applies even more to the risks of dying between non-metastatic vs. metastatic patients in the current setting. Moreover, in section 3.16 of the current ACD, the committee criticises that "all patients with metastatic disease in the model had the same rate of death before, during and after docetaxel for metastatic disease". Whereas a Markov approach allows the user to explore scenarios with varying rates of death in the different health states, a PartSA approach does not. • The Markov and PartSA approaches are merely modelling techniques that divide the model population over the different health states. Starting from identical clinical data (e.g. survival curves in this case), PartSA and Markov models are expected to produce similar results, if modelling and fitting have been done appropriately (NICE DSU TSD19). In our model, all curves were extrapolated and fitted in accordance to NICE DSU TSD14. The results of the 'single OS curve' scenario #7 included in our submission is therefore expected to produce similar results to a PartSA model.	
6	**Section 3.16** – It is more appropriate to use metastasis-free survival rather than time to stopping treatment with the second interim analysis **Section 3.17** – It is more appropriate to use data for overall survival from the second rather than the first interim analysis Taken individually, both of the above-mentioned opinions seem logical. It is, however, important to realise that survival endpoints (e.g. MFS and OS) are not structurally independent and that there are a number of dependencies between these measures (NICE DSU TSD19). For example, any pre-progression death contributes to both the MFS and OS endpoint, death cannot be followed by metastasis... etc. Therefore, mixing data from different data cuts (e.g. MFS from IA1 and OS from IA2) introduces structural and methodological problems to the economic analysis that likely outweigh any benefit of using slightly more mature OS data. This view was supported by independent expert advice we	The company are correct to note that the ERG were cautious about combining the MFS data (at IA1) with survival data from IA2, due to the inconsistencies the company refer to; i.e. using MFS data from the original cut in combination with OS split by time to treatment discontinuation from the later cut (IA2). However, whilst we did not state it was our base case, the ERG did tend towards favouring the analysis combining MFS with pre and post treatment discontinuation data from IA2.

	obtained before submission (reference #72 of Document B). Moreover, the ERG raised similar concerns and were hesitant to combine MFS data with survival data from IA2 (section 5.3.2 and 5.4 of the ERG report). Therefore, we believe that it was appropriate to combine MFS and IA1 OS data in our base case analysis, with an exploratory scenario combining time to treatment discontinuation (TTD) and OS data from IA2 in our submission.	These issues are discussed in detail in section 5.3.2 (reflection of the ERG preferred assumptions, paragraph 3, p116-117) of the ERG report. We conclude as follows: "*Therefore, the ERG has a preference towards the analysis which uses the MFS data from IA1 and the preTD and postTD survival data from IA2. Whilst the ERG recognise that there is an inconsistency between the measure used for progression (MFS), and the measure used to split the survival data in this scenario, the ERG prefer it because: 1) it uses the more robust measure of progression to metastasis; 2) it generates a more modest survival benefit in favour of enzalutamide in comparison with the base case. The ERG believe point 2 is appropriate given the lack of a significant difference in OS between the treatment arms of PROSPER at IA1 and IA2.*"
7	**Section 3.19 -** The committee concluded that there was a disconnection between observed and modelled overall survival in both the company's and ERG's model All parametric survival functions used in our model were constructed on the basis of, and fitted to, PROSPER patient-level data for the within-trial period and extrapolated beyond the trial observation period, as per NICE DSU TSD14 and good practice guidelines on survival analysis. The median OS in the model's base-case analysis for the ADT group was estimated around 48 months, which is consistent with historic median OS data observed in the placebo control arms of clinical studies in similar populations reported by Nelson et al (46.1 months) and Smith et al (44.8 months). It has been shown that the pre-metastasis death rates are not driving the model's outputs, which is consistent with the fact that non-metastatic patients are unlikely to die from prostate cancer. With regard to post progression survival data, the ERG mentioned that "it is reassuring to note that extrapolation... has been externally	It is correct that so say that the ERG noted "it is reassuring to note that extrapolation... has been externally validated against OS data from the PREVAIL trial". However, this only really applies to extrapolation of post progression survival of the ADT arm of PROSPER – which was validated against the enzalutamide arm of PREVAIL. It is less appropriate to use the PREVAIL trial placebo arm to guide extrapolation of PPS in the enzalutamide arm of PROPSER, because the PREVAIL placebo arm represented an

	validated against OS data from the PREVAIL trial". Together with the arguments we already presented in comment #1 of this table, these elements strengthen our belief that the estimates produced by our model are realistic and clinically plausible. References: - Nelson JB, Love W, Chin JL, Saad F, Schulman CC, Sleep DJ, Qian J, Steinberg J, Carducci M; Atrasentan Phase 3 Study Group. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer. 2008 Nov 1;113(9):2478-87. doi: 10.1002/cncr.23864. - Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, Tombal B, Damiao R, Marx G, Miller K, Van Veldhuizen P, Morote J, Ye Z, Dansey R, Goessl C. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol. 2013 Oct 20;31(30):3800-6. doi: 10.1200/JCO.2012.44.6716.	enzalutamide naïve cohort who could still receive it at a later treatment line (post-chemotherapy).
8	**Section 3.26** - Enzalutamide plus ADT is not cost effective compared with ADT alone. The ERG presented a base-case ICER of £56,168 per QALY gained We have several concerns about the information presented in this section of the ACD, including: • As explained in comment #6, combining MFS from IA1 with OS data from IA2 in the economic analysis is methodologically problematic because these two endpoints are structurally dependent. The ERG has recognised that such an approach is inconsistent (ERG report section 5.3.2) and has stated that "The ERG preferred set of assumptions are incorporated in scenario #7" (ERG report section 5.3.2 and Table 33). ERG scenario #7 indeed combines MFS data with OS data from IA1 and results in an ICER of £35,628 per QALY gained. Nevertheless, the committee has presented ERG scenario #9, combining MFS with IA2 OS data and resulting in an ICER of £56,168 as "the base case ICER presented by the ERG" (ACD section 3.26) • Both ERG scenarios #7 and #9 use a utility value of 0.844 previously obtained from the PREVAIL study (section 5.2.7 and table 33 of the ERG report and TA377), although the committee considers the utility value derived from PROSPER to be more appropriate because it used the same source of clinical data (ACD section 3.23) • An economic analysis combining the ERG preferred assumptions #2, #4 and #7 (equalised monitoring and testing frequencies, MACE costs increased to £3,279, and median duration in	• It is correct that the ERG report did not explicitly state our base case ICER to be £56,168 per QALY gained. The ERG did recognise inconsistencies in the analysis combining MFS from IA1 and OS data by treatment discontinuation from IA2. However, as noted above (see response to point 6), we did come down in favour of this analysis because of 1) the limitations of using time to treatment discontinuation to approximate time to metastatisis; and 2) it generated lower survival gains which appeared more consistent with the Kaplan Meier curves from IA2. • Both Scenario 7 and 9 did use the

	PD1 following progression on enzalutamide of 3.8 months) with the committee preferred utility value for the PD1 health state, and IA2 data for TTD, pre- and postTD survival, results in an ICER of £27,800 per QALY gained and suggests that enzalutamide could be considered both clinically beneficial and cost-effective in this setting.	preferred ERG utility value of 0.844, for reasons outline in our report. • The analysis assumptions described in bullet point 3 do generate an ICER of 27,800. The ERG disagree with the use of TTD from IA2 as proxy for progression to metastasises, for the reasons summarised in section 5.3.2 or our report (paragraph 3, page 116): "*the ERG are concerned that the TTD data is only a proxy for progression to mHRPC, which may be susceptible to bias; i.e. if patients are more likely to discontinue placebo as opposed to active treatment prior to radiographic progression, then the TTD curves may overestimate the rate of progression to mHRPC for ADT patients. Alternatively, if patients are less likely to discontinue enzalutamide immediately following progression to metastasis, then the TTD may underestimate true progression in the enzalutamide arm*."

Insert extra rows as needed

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

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