NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

Enzalutamide for hormone-relapsed non-metastatic prostate cancer

1 Recommendations

1.1 Enzalutamide is not recommended, within its marketing authorisation, for treating high-risk hormone-relapsed non-metastatic prostate cancer in adults.

1.2 This recommendation is not intended to affect treatment with enzalutamide that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Currently, when prostate cancer no longer responds to hormone treatment (androgen deprivation therapy), but has not yet spread beyond the prostate, the only option is to continue hormone treatment. The company proposes using enzalutamide in this setting.

Clinical trial evidence shows that adding in enzalutamide extends the time until the cancer starts spreading to other parts of the body. But there is no evidence that it increases how long people live.

Cost-effectiveness estimates comparing enzalutamide plus androgen deprivation therapy with androgen deprivation therapy alone are uncertain. This is because:

- it is not possible to estimate accurately how long people who take enzalutamide live
- the costs and benefits of treatments used after enzalutamide in the economic analysis do not reflect NHS practice.

The estimates are not within the range that NICE usually considers a cost-effective use of NHS resources. Therefore, enzalutamide is not recommended in the NHS for treating hormone-relapsed non-metastatic prostate cancer.

2 Information about enzalutamide

Marketing authorisation indication	Enzalutamide (Xtandi, Astellas) has a marketing authorisation 'for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer'.
Dosage in the marketing authorisation	Enzalutamide is administered orally at a dose of 160 mg (4x40 mg soft capsules) daily.
Price	£2,734.67 per 112 capsules (excluding VAT; British national formulary online, accessed December 2018) The daily dose comprises 4 capsules and costs £97.67. The company has a commercial arrangement which would apply if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Astellas and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Treatment pathway

The company places enzalutamide earlier in the treatment pathway than existing indications

3.1 The committee noted that there are different clinical circumstances in which people with prostate cancer may have treatment. These are broadly defined by whether the cancer is hormone sensitive or hormone relapsed,

and whether it has spread (metastasised) or not. This appraisal focuses on enzalutamide for hormone-relapsed non-metastatic prostate cancer. The clinical experts noted that this group is small and becoming smaller. This is because improved, more sensitive, radiographic imaging means that there are fewer people with undetected metastases who would otherwise be labelled as having non-metastatic disease. NICE technology appraisal guidance already recommends enzalutamide for hormone-relapsed metastatic prostate cancer before and after treatment with docetaxel. This appraisal relates to using enzalutamide at an earlier point in the treatment pathway. The committee noted that NHS England's policy stipulates that either enzalutamide or abiraterone (another antiandrogen) is to be offered only once in the treatment of prostate cancer. Therefore, using enzalutamide at this earlier position in the treatment pathway would mean that neither it nor abiraterone would be an option later (either before or after chemotherapy) once the cancer has metastasised.

Experience of people with prostate cancer

Prostate cancer causes few symptoms until metastases occur

3.2 Patient experts commented that most people with hormone-relapsed non-metastatic prostate cancer have no or few symptoms. Those who have symptoms experience mainly urinary difficulties. Symptoms increase when metastases develop. For example, bone and visceral metastases may cause pain and visceral metastases may cause site-specific symptoms. The committee noted that patients consider there to be an unmet need for treatments that delay metastasis.

Clinical management

Androgen deprivation therapy is the relevant comparator in this appraisal

3.3 Androgen deprivation therapy (ADT) has long been the standard of care for treating prostate cancer. The clinical experts explained that ADT is continued throughout the treatment pathway, even when the cancer

becomes hormone relapsed. This is because stopping treatment may speed up metastasis. The clinical experts commented that bicalutamide and dexamethasone are sometimes used for hormone-relapsed non-metastatic disease, but that the evidence for their effectiveness is limited. The committee considered ADT to be the standard of care in patients with hormone-relapsed prostate cancer, and the relevant comparator in this appraisal.

The company's definition of high risk does not closely match what is considered high risk in clinical practice

3.4 The company's decision problem focused on the subset of people with hormone-relapsed non-metastatic prostate cancer whose disease is at 'high risk' of metastasis, defined as:

- an absolute prostate-specific antigen (PSA) level of 2 ng/millilitre or more
- a PSA doubling time of 10 months or less.

This definition reflects the inclusion criteria in the key trial for enzalutamide (see section 3.5) and the marketing authorisation. NICE's guideline on prostate cancer: diagnosis and management recommends starting ADT if the PSA doubling time is less than 3 months in the hormone-sensitive setting. The clinical experts commented that, when assessing risk, clinicians take into account PSA doubling time but also other factors such as the age and fitness of patients. They advised that a clinically meaningful PSA doubling time in this setting would be less than 6 months. The committee concluded that clinicians' definition of people with high-risk disease in clinical practice does not closely match the patients the company defined as having high-risk disease. Although this was a source of uncertainty, the committee did not expect it to affect the generalisability of clinical results from 1 group to the other.

Clinical evidence

The PROSPER trial provides the main clinical evidence for enzalutamide

3.5 The main evidence for enzalutamide came from PROSPER, a double-blind randomised placebo-controlled trial. It included 1,401 patients with high-risk hormone-relapsed non-metastatic cancer, allocated to either enzalutamide plus ADT (n=933) or placebo plus ADT (n=468). The primary outcome was metastasis-free survival, defined as the time to radiographic evidence of metastasis or death, whichever occurred first. Scans were done every 16 weeks, or sooner if metastatic disease was suspected. Secondary outcomes included overall survival, quality of life, time to stopping treatment and safety.

The population in PROSPER has lower-risk disease but is otherwise similar to patients in the NHS who may have enzalutamide

3.6 The clinical experts advised that, apart from the criterion for PSA doubling time (see section 3.4), patients in PROSPER were generally like people who would be offered enzalutamide in the hormone-relapsed non-metastatic setting in clinical practice. The committee noted that some patients had a PSA doubling time greater than 10 months (which the study protocol did not allow), or a serum PSA higher than would be expected in the non-metastatic setting. The ERG commented that few patients did not meet the selection criteria and so were unlikely to have biased the results. The committee concluded that the population in PROSPER was sufficiently generalisable to NHS clinical practice.

Enzalutamide increases metastasis-free survival

3.7 The median metastasis-free survival with enzalutamide was 36.6 months compared with 14.7 months for placebo (hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.24 to 0.35; p<0.0001) based on the final analysis. The committee agreed that enzalutamide was more effective than placebo at delaying metastasis.

The overall survival data are immature

3.8 The company presented 2 of 3 planned interim analyses of overall survival: the first after 135 deaths (coinciding with the final analysis for metastasis-free survival; see section 3.7), and the second after 285 deaths (about 1 year later). The company stated that it intends to do another interim analysis and a final analysis. The committee appreciated that, in its amended statistical plan, the company planned the final analysis for when 596 deaths had occurred. It agreed that the overall survival data from PROSPER presented by the company were immature and provided too few deaths to detect a statistically significant difference between treatment arms. For example, at the second interim analysis, the median overall survival had not been reached and the hazard ratio between the 2 treatment arms was not statistically significant as predefined (HR 0.83, 95% CI 0.65 to 1.06; p=0.134). In response to consultation, the company agreed that the overall survival data were immature because the study was statistically powered to detect a benefit in metastasis-free survival rather than overall survival. The committee noted this comment but agreed that overall survival was clinically important and key to populating the economic model.

Enzalutamide has not been shown to prolong life in patients with high-risk hormone-relapsed non-metastatic prostate cancer relative to placebo

3.9 The committee noted that the data did not show that enzalutamide plus ADT confers a survival benefit relative to ADT, acknowledging that the hazard ratio should be interpreted with caution because the data violate the proportional hazard assumption. The committee queried whether the lack of survival benefit could be explained by patients in the placebo arm being offered active therapies such as enzalutamide after metastasis and then 'catching up' with those randomised to enzalutamide earlier who had also progressed. The clinical experts stated that there was not enough evidence to comment on this. The committee also queried whether the effect of enzalutamide plus ADT relative to ADT alone decreased towards

the end of the trial follow up, having observed that patients initially randomised to enzalutamide were more likely to stop life-extending subsequent therapies. The clinical experts suggested that this was unlikely. The committee concluded that the latest evidence available did not show a survival benefit with enzalutamide relative to placebo for hormone-relapsed non-metastatic prostate cancer. In response to consultation, the company suggested that it was difficult to show a statistically significant benefit in this population because, over time, people may die from causes other than prostate cancer. However, the committee agreed that, in a randomised trial, mortality from causes other than prostate cancer would be similar in both treatment arms. In the absence of new evidence, the committee did not change its conclusions about enzalutamide's survival benefit compared with placebo.

Enzalutamide may be less effective in terms of overall survival, both absolutely and relatively, when used earlier in the treatment pathway

3.10 The committee discussed whether the relative effectiveness of enzalutamide at later points in the treatment pathway could provide insight into its survival benefit in the hormone-relapsed non-metastatic setting. In this setting (see section 3.8), the hazard ratio for overall survival was 0.83 (95% CI 0.65 to 1.06). This compared with hazard ratios later in the treatment pathway (that is, for hormone-relapsed metastatic disease) of 0.76 (95% CI 0.66 to 0.88) in the pre-chemotherapy setting and 0.62 (95% CI 0.52 to 0.73) in the post-chemotherapy setting. Assuming that the hazard ratio of 0.83 was a valid estimate (see section 3.9), the committee queried the differences in absolute benefit with enzalutamide along the treatment pathway. The clinical experts explained that, for hormone-sensitive prostate cancer, there was some evidence that abiraterone and docetaxel may provide greater benefit if used earlier in the pathway, but there was no such evidence for enzalutamide. For hormone-relapsed disease, they highlighted the unclear relationship between the timing of enzalutamide treatment and overall survival. However, they agreed that

the absolute benefit with enzalutamide was larger after chemotherapy than before. The committee acknowledged concerns with the validity of the hazard ratio for overall survival (see section 3.8). It agreed that, if enzalutamide does prolong life, the evidence to date suggests that the benefit is lower when offered earlier than later in therapy. 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.

Subsequent treatments in PROSPER confound overall survival

3.11 The company presented information on the treatments used after metastasis for each treatment arm in PROSPER. The committee noted that:

- Some patients in the enzalutamide plus ADT arm had further treatment with abiraterone and enzalutamide, which would not be available in NHS clinical practice and for which there may be a survival benefit.
- Some patients in both arms had treatments not used in the NHS, which may be associated with a survival benefit (for example, sipuleucel-T).
- The distribution of subsequent therapies differed between treatment arms after metastasis, with a larger proportion of patients in the enzalutamide arm having no active therapies, and a larger proportion in the placebo arm having enzalutamide, abiraterone and docetaxel.

The committee agreed that the subsequent therapies used in PROSPER meant that the relative effectiveness of enzalutamide in clinical practice is unlikely to reflect the reported effect in PROSPER. The committee concluded that the company should have adjusted for the effect of both life-extending subsequent treatments not available in the NHS and of life-extending subsequent treatments available in the NHS but which were used more frequently in PROSPER. In response to consultation, the company maintained that it did not need to adjust for the sequential use of enzalutamide and abiraterone because there was no evidence of a

survival benefit. Although the committee accepted this possibility, it remained concerned that the proportion of patients randomised to placebo with ADT who had subsequent therapies differed from the NHS. The committee acknowledged that there is no straightforward method to adjust for this and recognised that it would remain an area of uncertainty, which the company could explore in scenario analyses by varying its assumptions about long-term treatment effects.

Quality of life

The relationship between enzalutamide and quality of life is not appropriately modelled

3.12 The patient experts explained that they had no problems with any aspect of their quality of life while having enzalutamide over several years. The company presented health-related quality-of-life data from PROSPER measured after 22 months of follow up using various quality-of-life instruments. These included the Brief Pain Inventory, the European Organisation for Research and Treatment of Cancer prostate cancer module (EORTC), Functional Assessment of Cancer Therapy – Prostate (FACT-P) and the EQ-5D. The only statistically significant ($p<0.05$) differences between treatments were detected using the EORTC in hormonal-treatment related symptoms and the FACT-P social wellbeing instruments. The committee concluded that there was not enough evidence from PROSPER to show that enzalutamide improved quality of life compared with placebo. In response to consultation, the company stated that enzalutamide increased the time until deterioration of quality of life compared with placebo rather than improving quality of life. The committee noted that data from PROSPER supported this, but that the company did not reflect this benefit in its economic model.

Company's economic model

The model has a semi-Markov partitioned survival structure

3.13 The company developed a semi-Markov partitioned survival model to assess the cost effectiveness of enzalutamide plus ADT compared with ADT alone. The model contained 3 states: hormone-relapsed non-metastatic, hormone-relapsed metastatic and death. The company used a partitioned survival model, informed by data from PROSPER, to model the transition of patients from the non-metastatic to the metastatic state, and from the non-metastatic or metastatic state to death. Within the metastatic state, the company used a Markov model with 3 sub-states (progressed-disease states 1 to 3) to capture disease progression beyond metastasis, and associated treatment options, costs and utilities. To model the transitions of patients within this state, the company used data from other trials, namely PREVAIL (enzalutamide compared with placebo in the pre-chemotherapy metastatic setting) and TAX-327 (docetaxel compared with mitoxantrone in the metastatic setting).

The company's model structure introduces additional uncertainty by splitting overall survival

3.14 The company chose a model structure in which overall survival needed breaking down into death before or after metastasis to align the data with the model states. However, this increased uncertainty in the model. The company stated that it chose this model structure to reflect clinical practice. The committee considered that the company did not sufficiently justify using a model structure that increased uncertainty. The company provided a scenario analysis using a single overall survival curve; however, this did not use the latest data available on overall survival. The scenario analysis was a useful approximation of the standard 3-state partitioned survival model. However, the committee considered that the company should have at least validated the output of its model against the 3-state partitioned survival model commonly used in oncology, and on

which NICE's Decision Support Unit provides guidance. The committee concluded that the model structure chosen by the company unnecessarily introduced additional uncertainty to the model's outputs.

There is no evidence to support that enzalutamide prolongs life before disease metastasises

3.15 To model death rates before disease metastasis, the company extrapolated pre-progression survival from PROSPER beyond the follow-up period of the trial. This was based on a few patients who died before metastasis, and the diverging curves translated to a large absolute benefit for enzalutamide compared with ADT. The clinical experts explained that the death rate pre-metastasis was likely to reflect the mortality of the general population because people are unlikely to die from non-metastatic prostate cancer. The committee agreed that the company's modelling of pre-progression survival lacked face validity and was likely to bias results in favour of enzalutamide.

Post-progression survival is biased

3.16 The committee noted that the company's extrapolation of post-metastasis survival did not preserve randomisation in PROSPER because most patients in the ADT arm, but only half of those in the enzalutamide arm, developed metastasis. This introduced selection bias because the extrapolation of the enzalutamide arm was based only on patients whose disease metastasised early (relative to the median time to metastasis), whereas the extrapolation of the ADT was based on almost all patients whose disease metastasised. It also meant that the extrapolation was based on disproportionate numbers at risk between the 2 arms. The committee agreed that this approach divided immature data in inappropriate ways and introduced bias.

Survival in each progressed-disease state is likely to differ

3.17 The company used PROSPER to model the transition from the metastatic state to death. This was constant over time and so the company implicitly

assumed that all modelled patients with metastatic disease had the same rate of death before, during and after docetaxel treatment for metastatic disease. The clinical experts advised that this was implausible because they would expect to see a lower death rate in early metastatic disease than after chemotherapy. The company's assumption of equal instead of lower death rates in the early metastatic sub-state disproportionately affected the survival rates of patients having ADT, who moved to the metastatic state faster than those having enzalutamide. The committee concluded that the company's model structure and assumptions biased survival in favour of enzalutamide.

It is better to use data for overall survival from the second rather than the first interim analysis

3.18 The company used results for time to death (overall survival) in its base case from the first of 4 planned analyses to coincide with the final analysis of metastasis-free survival. However, the committee preferred using overall survival from the second interim analysis (see section 3.8) because the data, although immature, were more mature than from the first interim analysis.

The lack of data on time to metastasis at the time of the second interim analysis of overall survival is a limitation of the modelling

3.19 To estimate the time patients spent before their disease metastasised and the time they spent before they died, the company presented 2 scenarios. The first (company's base case) used metastasis-free survival from the final analysis of metastasis-free survival, and overall survival from the first interim analysis of overall survival (which coincided with the final analysis of metastasis-free survival). The second scenario used time to stopping treatment (as a proxy for metastasis-free survival) and overall survival, both from the time of the second interim analysis for overall survival. The ERG commented that it was uncertain how long people stayed on treatment after metastasis. It preferred time to metastasis (only available from the time of the first interim analysis of overall survival) over time to

stopping treatment to model the time patients spend before their disease metastasises. The committee agreed with this, also noting that metastasis-free survival was the protocol-defined primary outcome of the trial and reflected the health state in the model. It also recalled that it preferred overall survival from the second interim analysis (see section 3.18). However, the company, in response to consultation, noted that using time to metastasis (from the 1 analysis that analysed it) and overall survival from the second interim analysis meant that time to stopping treatment had to be used to spilt overall survival. This was because it split overall survival into pre- and post-progression survival and because PROSPER did not report time to metastasis at the time of the second interim analysis of overall survival. The committee agreed that this introduced methodological issues. It also meant the timings of the data-cuts constrained the company to forever modelling events from the time of the first interim analysis of overall survival despite ongoing data collection. The committee considered this to be irrational. The committee maintained its preferences for time to metastasis to model the time patients spent before their disease metastasises, and for the most mature overall survival data to model the time people spend alive. However, it appreciated the limitations of its preferences. These arose from the lack of time to metastasis data from the time of the second interim analysis of overall survival, and from having to use time to stopping treatment to split overall survival into pre- and post-progression survival.

The company's modelled output does not match what occurred in PROSPER

3.20 The company used the survival data from the first interim analysis to generate a model, which showed that the rate of death in the ADT arm differed from, and increased more quickly than, that in the enzalutamide arm. This meant that the relative effectiveness of the treatments in the enzalutamide arm on overall survival continued to improve over time (the hazard ratio decreased). This modelled survival did not correspond with the latest data for overall survival seen in PROSPER, which showed no

survival benefit (see section 3.8). The ERG used data for overall survival from the second interim analysis. This resulted in the relative effectiveness for survival of the treatments in the enzalutamide arm improving for up to 8.7 years (hazard ratio decreasing), then waning over the following 8.0 years (hazard ratio increasing to 1) and then reversing (hazard ratio greater than 1). The committee appreciated that, although this was a more reasonable assumption than the company's, it still did not reflect the observed data. It concluded that there was a disconnect between observed and modelled overall survival in both the company's and ERG's models.

Treatment sequence in the economic model

The economic model should include cabazitaxel and radium-223

3.21 The company modelled a treatment sequence based on what the company's clinical expert expected in NHS clinical practice, and applied costs to these treatments. This assumed that everyone starting on enzalutamide had ADT after developing metastases ('progressed-disease state 1'; see section 3.12) and vice versa. In progressed-disease state 2, 40% of people in both arms of the model had docetaxel and 60% had ADT alone. In progressed-disease state 3, everyone in both arms had best supportive care (which included ADT). The committee discussed the sequence of treatments that best reflected NHS practice, appreciating that:

- enzalutamide would be continued for longer in clinical practice than it was in PROSPER because radiographic progression to determine metastasis is not measured as frequently in clinical practice as it was in PROSPER, and because clinicians may offer treatment beyond metastasis in certain clinical circumstances
- abiraterone and enzalutamide are used in approximately equal proportions in the pre-docetaxel setting (corresponding to the modelled progressed-disease state 1)

- clinical experts consider that more than 40% of patients will be fit enough to have docetaxel when symptoms appear
- about 20% of patients who have treatment in the post-docetaxel setting have cabazitaxel
- radium-223 is considered for patients with bone metastatic disease and is used only with ADT.

The committee agreed that enzalutamide is likely to be continued for longer in practice than in the trial, which would increase the cost of treatment. However, it considered that it was inappropriate to include the cost of enzalutamide based on a longer treatment. This was because longer treatment might also be associated with higher effectiveness, which would be difficult to model. In general, the committee concluded that an appropriate treatment sequence should have included cabazitaxel and radium-223.

The modelled sequence of treatments does not match the observed sequence of treatments in PROSPER

3.22 The committee appreciated that the company modelled the costs of treatments for patients with metastatic disease. However, the therapies for metastatic disease as modelled do not reflect what happened in PROSPER. For example, only 11% of patients with progressed disease in placebo arm of PROSPER had enzalutamide at follow up, compared with 100% in the economic model. The committee concluded that dissociating costs and effectiveness in the economic model biased the estimates of cost effectiveness in favour of enzalutamide.

Treatment duration in the economic model

For people having enzalutamide, the time spent in the first progressed-disease state is unlikely to be as long as that modelled by the company

3.23 In its base case, the company assumed that patients whose cancer metastasised having had enzalutamide would remain in the first

progressed-disease state (pre-chemotherapy) for 7.3 months, based on the PREVAIL trial (enzalutamide compared with placebo in the pre-chemotherapy metastatic setting). The ERG was concerned that the population of PREVAIL was not generalisable to the population of PROSPER because PROSPER included only patients with a high risk of progression to metastasis at baseline. The clinical experts agreed that 7.3 months was an implausibly long amount of time to have ADT alone in the metastatic state. The ERG proposed a scenario using the time between metastasis and first use of active treatment seen in the enzalutamide arm of PROSPER, which led to a shorter time. The committee agreed with the ERG's approach.

Utility values in the economic model

The utility value for the first metastatic progressed-disease state should come from PROSPER

3.24 The company used EQ-5D data collected in PROSPER to inform the utility value in the economic model for the first progressed-disease state. The ERG considered the company's choice of utility value for this state to be lower than expected, considering people have few symptoms. It considered the baseline utility from PREVAIL, which measured utility in the metastatic pre-chemotherapy setting, to be more representative of people at this stage of the disease. The committee acknowledged the uncertainty around the utility estimate for the first metastatic progressed-disease state. However, it considered the utility value derived from PROSPER to be more appropriate because the model then used the same source for both utility and clinical data.

Costs in the economic model

The costs of monitoring disease would be the same whether people have enzalutamide plus ADT or ADT alone

3.25 The company presented higher monitoring costs for people having ADT alone compared with people on enzalutamide plus ADT within the model. The clinical experts said that the frequency of monitoring would not differ, a conclusion shared by the ERG's clinical expert. The ERG presented a scenario that equalised the monitoring frequencies and costs between both arms. The committee concluded that the ERG's scenario was appropriate.

The costs of major adverse events are not included appropriately

3.26 The committee was concerned that the company's model did not fully reflect the costs of major adverse events. Significant adverse events that occurred substantially more often with enzalutamide than with placebo in the trials included hypertension, memory impairment and major adverse cardiovascular events. The clinical experts also noted that fatigue and osteoporosis are common adverse effects with enzalutamide. The ERG noted that the company did not model costs for memory impairment or explore costs associated with osteoporosis. It was also concerned that the costs of major adverse cardiovascular events were not included appropriately considering the higher incidence of these events in patients having enzalutamide. The company used the costs of non-elective short stays for all major adverse cardiovascular events, but most events were coded as long stays. The company confirmed that it did not include the costs associated with rehabilitation from strokes. The ERG presented a scenario that included the costs of the total distribution of lengths of inpatient stays, which substantially increased the costs of major adverse cardiovascular events. The company agreed with this. The committee concluded that the scenario with increased costs was appropriate.

Cost-effectiveness estimates

Enzalutamide plus ADT is not cost effective compared with ADT alone

3.27 The committee considered whether enzalutamide would be a cost-effective use of NHS resources for non-metastatic hormone resistant prostate cancer, taking into account the patient access scheme (discount) associated with enzalutamide. The company presented a base-case deterministic incremental cost-effectiveness ratio (ICER) of £28,853 per quality-adjusted life year (QALY) gained. However, this value was uncertain and included several assumptions that the committee considered inappropriate, notably, that enzalutamide prolongs survival when used in non-metastatic disease. The ERG presented a base-case ICER of £56,168 per QALY gained, which included:

- using data on overall survival from the second interim analysis (see section 3.17)
- modelling less time spent in the first progressed-disease state for patients in the enzalutamide arm (see section 3.22) than modelled by the company
- increasing baseline utility in the first progressed-disease state (see section 3.23) compared with the company's value
- correcting the company's costs (see sections 3.24 and 3.25).

The committee concluded that most of the ERG's changes to the company's model were appropriate. It noted that the ERG's ICERs may even have been low because they did not include the costs of radium-223 and cabazitaxel. Also, the ERG's model did not reflect the absence of an overall survival benefit for enzalutamide in the trial (see section 3.8). The committee noted that the ERG provided a scenario that included the costs of cabazitaxel and radium-223, both associated with confidential discounts, which increased the ICERs. The committee reiterated that both the company's and ERG's ICERs were associated with substantial uncertainty. This mainly arose from: the immaturity of the overall survival

data; the lack of evidence of a survival benefit or quality-of-life improvement by delaying metastasis; and the disconnect between the costs and benefits of subsequent treatments in the model. Furthermore, splitting survival into before and after metastasis in the model introduced an additional layer of uncertainty. It concluded that enzalutamide could not be recommended as a cost-effective use of NHS resources for hormone-relapsed non-metastatic prostate cancer.

Other factors

The health benefits associated with enzalutamide are captured

3.28 The company noted that this is the first indication for a drug within the high-risk non-metastatic prostate cancer population. However, the committee agreed that this was not associated with additional gains in health-related quality of life over those already included in the QALY calculations.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
April 2018

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Adam Brooke
Technical Lead

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