NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Enzalutamide for treating hormone-sensitive metastatic prostate cancer

1 Recommendations

1.1 Enzalutamide plus androgen deprivation therapy (ADT) is recommended, within its marketing authorisation, as an option for treating hormone-sensitive metastatic prostate cancer in adults. It is only recommended if the company provides enzalutamide according to the agreed commercial arrangement (see section 2).

Why the committee made these recommendations

Current treatment for hormone-sensitive metastatic prostate cancer in the NHS is ADT alone, or docetaxel plus prednisolone or prednisone (from now, docetaxel) plus ADT. Enzalutamide plus ADT would offer another option for people with hormone-sensitive metastatic prostate cancer, especially for people who cannot have docetaxel. It is taken by mouth so is more convenient than docetaxel, which is an intravenous treatment.

Trial results suggest that, compared with ADT alone, enzalutamide plus ADT increases the time until the cancer progresses and how long people live. Also, an indirect comparison suggests that, compared with docetaxel plus ADT, enzalutamide plus ADT increases the time until the cancer progresses. But, it is unclear whether there is a difference between the 2 treatments in the length of time people live.

The cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources. Therefore, enzalutamide plus ADT is recommended for hormone-sensitive metastatic prostate cancer.

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2 Information about enzalutamide

Anticipated marketing authorisation indication

2.1 Enzalutamide (Xtandi, Astellas) has an anticipated marketing authorisation in the UK for 'the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy'.

2.2 On 25 March 2021, the Committee for Medicinal Products for Human Use adopted a positive opinion recommending a variation to the terms of the marketing authorisation for enzalutamide, which was for 'the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT)'.

Dosage in the marketing authorisation

2.3 The dosage schedule is available in the summary of product characteristics.

Price

2.4 The list price of a 112-capsule pack of 40 mg enzalutamide is £2,734.67 (excluding VAT; BNF online, accessed May 2020). The daily dose of enzalutamide is 160 mg and costs £97.67.

2.5 The company has a commercial arrangement (commercial access agreement). This makes enzalutamide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Astellas, the company that markets enzalutamide, a review of this submission by the evidence

review group (ERG), the technical report prepared by NICE and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage. It agreed that there should be a total utility decrement of 0.093 across the hormone-relapsed health sub-states (issue 7 page 26 of technical report). It discussed the issues that were outstanding after the technical engagement stage.

Clinical need and clinical management

People with hormone-sensitive metastatic prostate cancer would welcome the option of treatment with enzalutamide

3.1 The clinical and patient experts noted that people with hormone-sensitive metastatic prostate cancer have limited treatment options. NICE's guideline for prostate cancer recommends androgen deprivation therapy (ADT) alone, and docetaxel with prednisolone or prednisone (from now, docetaxel) plus ADT. Docetaxel is not licensed for hormone-sensitive metastatic prostate cancer, but NHS England commissions it for up to 6 cycles. The patient experts explained that, when people are first diagnosed with metastatic prostate cancer, they may have no or few symptoms. They also explained that some people perceive that treatment with docetaxel worsens quality of life and choose to have ADT alone, even though the long-term outcomes may be worse than with docetaxel plus ADT. So, because enzalutamide plus ADT is generally better tolerated than docetaxel plus ADT, and is more effective than ADT alone, people would welcome it as an option at this point in the treatment pathway. The committee concluded that some people with hormone-sensitive metastatic prostate cancer would welcome the option of treatment with enzalutamide plus ADT.

Temporary guidance on enzalutamide for hormone-sensitive metastatic prostate cancer will be superseded by this appraisal's recommendations

3.2 NICE's rapid guideline on the delivery of systemic anticancer treatments during the COVID-19 pandemic aims to:

- maximise the safety of patients with cancer
- make the best use of NHS resources
- protect staff from infection
- enable services to match the capacity for cancer treatment to patient needs if services become limited because of the COVID-19 pandemic.

The guideline provides a link to interim treatment change options, which are endorsed by NHS England. It includes the option of giving enzalutamide plus ADT instead of docetaxel to reduce toxicity and potential for hospital admission. Treatment regimens will revert to the standard commissioned position after this period unless the guideline is updated. Any interim treatment subject to an ongoing NICE technology appraisal will be superseded by an appraisal guidance.

ADT alone and docetaxel plus ADT are both relevant comparators

3.3 The committee was aware that the NICE scope included as comparators ADT alone and docetaxel plus ADT. The clinical experts explained that both are offered in the NHS to people with hormone-sensitive metastatic prostate cancer. The committee was also aware of the ongoing NICE technology appraisals for abiraterone plus ADT for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer and apalutamide plus ADT for hormone-sensitive metastatic prostate cancer. The committee concluded that neither abiraterone plus prednisone (from now, abiraterone) and ADT nor apalutamide plus ADT were comparators because they are not routinely commissioned at this point in the treatment pathway. The Cancer Drugs Fund's clinical lead noted that around two-thirds of people presenting with hormone-sensitive metastatic prostate cancer in England have ADT alone. Of these people, some are not fit

enough for docetaxel, and some choose not to have it because of its adverse events (see section 3.1). NHS England's docetaxel commissioning policy states that someone may not be fit enough for docetaxel if they have:

- a poor overall performance status (World Health Organization [WHO] performance 3 to 4)
- pre-existing peripheral neuropathy
- poor bone marrow function or
- a life-limiting illness.

The policy also states that docetaxel should be used with caution in people with a WHO performance status of 2, and that there are few absolute contraindications for docetaxel therapy. The committee concluded that ADT alone and docetaxel plus ADT were relevant comparators for people who could have docetaxel and ADT, and that ADT alone was the relevant comparator for people who could not have docetaxel. The committee recognised the importance of patient choice when all treatment options are clinically and cost effective.

The first treatment for hormone-sensitive metastatic prostate cancer affects the number of life-extending treatments people have later

3.4 Under NHS policy, people who have docetaxel plus ADT for hormone-sensitive prostate cancer for up to 6 cycles can have docetaxel again (for up to 10 cycles) for hormone-relapsed prostate cancer. This is because the benefit of docetaxel is not exhausted. Other treatment options for hormone-relapsed metastatic prostate cancer include both enzalutamide and abiraterone when chemotherapy is not yet clinically indicated, or after a docetaxel-based regimen. In summary, enzalutamide has a licence for 4 positions in the treatment pathway (including 1 for non-metastatic prostate cancer). However, the Cancer Drugs Fund clinical lead explained that NHS England commissions each of enzalutamide and abiraterone only once in the treatment pathway. This is because there is no evidence

of clinical benefit for using one after the other. It means that people who have enzalutamide plus ADT for hormone-sensitive metastatic prostate cancer cannot have enzalutamide or abiraterone later in the treatment pathway. It also means that people who have docetaxel plus ADT first for hormone-sensitive metastatic prostate cancer have more treatment options than people who have enzalutamide plus ADT first. This is because they can have either enzalutamide or abiraterone, and can also have docetaxel again. The sequence of follow-on treatments when the cancer is hormone-relapsed may vary from person to person. Possible treatments include:

- After ADT alone, or docetaxel plus ADT:
  - enzalutamide or abiraterone (before or after docetaxel)
  - docetaxel
  - other active treatments such as cabazitaxel or radium-223.
- After enzalutamide plus ADT:
  - docetaxel
  - other active treatments such as cabazitaxel or radium-223.

The committee concluded that the treatment choice for hormone-sensitive metastatic prostate cancer affects the treatments a person can have when the cancer is hormone-relapsed. It also concluded that having enzalutamide plus ADT at this point in the pathway limits the number of life-extending treatment options compared with having ADT alone or docetaxel plus ADT.

Clinical evidence

ARCHES and ENZAMET are both relevant trials for assessing the clinical effectiveness of enzalutamide plus ADT

3.5 Two randomised controlled trials, ARCHES and ENZAMET, have investigated the clinical effectiveness of enzalutamide plus ADT for treating hormone-sensitive metastatic prostate cancer:

- ARCHES was a double-blind trial including 1,150 people with hormone-sensitive metastatic prostate cancer. It compared enzalutamide plus ADT (n=574) with ADT alone (n=576). The primary endpoint was progression-free survival. Overall survival and health-related quality of life were secondary endpoints.
- ENZAMET was an investigator-led open-label trial including 1,125 people with hormone-sensitive metastatic prostate cancer. It compared enzalutamide plus ADT (n=563) with conventional non-steroidal anti-androgens (NSAAs) plus ADT (n=562). The primary endpoint was overall survival. Progression-free survival and health-related quality of life were secondary endpoints. People could have concomitant docetaxel, which is not included in the marketing authorisation for enzalutamide. Therefore, the company submission included data only from the 622 people who did not have concomitant docetaxel (309 in the enzalutamide plus ADT arm and 313 in the comparator arm).

The company had access to patient-level data for both trials. The trials differed by proportion of people with high-volume disease (see section 3.6), comparator (the control treatment) (see section 3.7), concomitant use of docetaxel and definition of progression-free survival (see section 3.8). The committee discussed these in turn. It concluded that both trials were relevant for assessing the clinical effectiveness of enzalutamide plus ADT for hormone-sensitive metastatic prostate cancer.

Patient characteristics in ARCHES and ENZAMET are broadly generalisable to NHS clinical practice

3.6 The baseline characteristics of the people in ARCHES and ENZAMET were similar. However, more people in ARCHES had Gleason scores equal to or greater than 8, or high-volume disease. The proportion of people with high-volume disease in ARCHES was similar to that in

STAMPEDE, an entirely UK-based trial assessing the best way to treat newly diagnosed advanced prostate cancer. The clinical experts agreed that people with high-volume disease have poorer prognoses than people with low-volume disease. However, they disagreed on whether disease volume modifies the relative effectiveness of treatment. One clinical expert noted that, in STAMPEDE, volume of disease did not alter treatment effectiveness. The committee noted that the evidence for enzalutamide plus ADT was based on a relatively fit population. It specifically excluded people with an Eastern Cooperative Oncology Group performance status of 2 or above, significant cardiovascular or renal disease, and other conditions. So, it may not be representative of some of the people who cannot have docetaxel. The committee appreciated that these issues could have added uncertainty to the results of the economic modelling. It concluded that the trials were broadly generalisable to NHS practice.

ENZAMET employs a comparator not used in the NHS, but the results of ARCHES and ENZAMET are appropriate for decision making

3.7 ARCHES compared enzalutamide plus ADT with ADT alone while ENZAMET compared it with conventional non-steroidal anti-androgens plus ADT. The committee highlighted that using non-steroidal anti-androgens does not reflect UK clinical practice and the company acknowledged this. However, the company did not think that it would affect the generalisability of the results to NHS clinical practice. The clinical experts confirmed that conventional non-steroidal anti-androgens are not used in the NHS in this setting. They explained that evidence suggested the combination may be more effective than ADT alone, but that adverse events are increased when adding non-steroidal anti-androgens to ADT. The committee concluded that the results of both trials were appropriate for decision making.

The definition of progression-free survival in ENZAMET more closely reflects NHS clinical practice than that in ARCHES

3.8 The 2 trials measured progression-free survival differently. In ENZAMET, it was defined based on clinical progression by radiographic imaging, symptoms attributable to cancer progression or starting another treatment for prostate cancer. This was broader than in ARCHES, in which progression-free survival was defined based on radiographic disease progression by an independent blinded and central review. The company chose only to model progression-free survival from ARCHES (see section 3.13). The clinical experts explained that there is more than a single way in clinical practice to assess progression-free survival, and that different centres might use different definitions. They confirmed that other measures might include serum prostate specific antigen. The committee concluded that it was appropriate to consider progression-free survival from both trials, and that the definition from ENZAMET better reflected NHS practice.

Enzalutamide plus ADT extends progression-free survival compared to ADT alone, or NSAAs plus ADT, but overall survival data is immature

3.9 The company presented data from planned final analyses for progression-free survival from ARCHES and ENZAMET. However, the trials are ongoing for the endpoint of overall survival. In ARCHES, enzalutamide plus ADT improved progression-free survival compared with ADT alone. The time to median progression-free survival was not reached for enzalutamide plus ADT and, for ADT alone, was 19 months. The hazard ratio was 0.39 (95% confidence interval [CI] 0.30 to 0.50). In ARCHES, cancer progressed in 16% of people in the treatment group and in 35% in the control group. In ENZAMET, enzalutamide plus ADT improved progression-free survival compared with conventional non-steroidal anti-androgens plus ADT (hazard ratio [HR] 0.34, 95% CI 0.26 to 0.44). The number of events was not available for ENZAMET. The median follow up was 14.4 month in ARCHES and 37.0 months in ENZAMET. At the same

time as doing final analyses for progression-free survival, the investigators did interim data analyses for overall survival. In ARCHES, 84 deaths had occurred at the time of the interim analysis out of the 342 deaths specified in the statistical analysis plan for the final analysis. In ENZAMET, 245 deaths had occurred at the time of the interim analysis out of the specified 470 deaths. At the time of the interim analysis, most people were still alive in both trials, and median overall survival could not be estimated in any treatment arm. Interim analyses from both trials suggested that enzalutamide plus ADT improved overall survival (ARCHES: HR 0.81, 95% CI 0.53 to 1.25; ENZAMET: HR 0.53, 95% CI 0.37 to 0.74). The confidence interval for the estimate from ENZAMET included the possibility of no effect. The company presented an analysis for overall survival based on unadjusted pooling of patient-level data from both trials. The committee did not support unadjusted pooling of results (see section 3.11). The ERG did not use the unadjusted pooled data to estimate overall survival. Instead, it modelled overall survival using hazard ratios from the company's network meta-analysis applied to the ADT-alone overall-survival curve. The committee concluded that enzalutamide plus ADT delayed time to progression compared with ADT alone, but that the data for overall survival were immature. This meant that the size of the overall benefit of enzalutamide plus ADT compared with ADT alone was uncertain.

Enzalutamide plus ADT extends progression-free survival compared with docetaxel plus ADT, but evidence on overall survival is uncertain

3.10 There are no trials that directly compare enzalutamide plus ADT with docetaxel plus ADT. The company did a network meta-analysis that included ARCHES and ENZAMET, 3 trials of docetaxel plus ADT compared with ADT alone (STAMPEDE1, CHAARTED and GETUG) and 6 trials of conventional non-steroidal anti-androgens plus ADT compared with ADT alone (DAPROC, EORTC 30853, INTERGROUP STUDY 0036, SWOG-8894, Janknegt 1993, Zalcberg 1996). The results suggested longer progression-free survival for enzalutamide plus ADT compared with

docetaxel plus ADT. For overall survival, the point estimate suggested a benefit for enzalutamide plus ADT but included the possibility of no effect. None of the results can be reported here because the company considers them confidential. The committee concluded that enzalutamide plus ADT extended progression-free survival when compared with docetaxel plus ADT, but evidence on overall survival was uncertain.

A network meta-analysis is better than unadjusted pooling to estimate effect on survival of enzalutamide plus ADT compared with ADT alone

3.11 The committee discussed the implications of pooling data from the 2 trials, ARCHES and ENZAMET, with different treatments for the control arm. It was aware that the company's network meta-analysis (see section 3.10) included 6 trials of conventional non-steroidal anti-androgens plus ADT compared with ADT alone. The results of the network also showed a benefit of non-steroidal anti-androgens plus ADT compared with ADT alone which included the possibility of no effect. To avoid using the pooled overall-survival data, the ERG estimated overall survival using hazard ratios from the company's network meta-analysis applied to the ADT-alone overall-survival curve. The committee concluded that, when comparing enzalutamide plus ADT to ADT alone, the network meta-analysis should inform the treatment effect for overall survival. It was aware that the data from ARCHES for ADT alone and ENZAMET for conventional non-steroidal anti-androgens plus ADT would still need to be pooled to provide a reference curve for applying treatment effect hazard ratios.

Cost effectiveness

The company's partitioned survival model is appropriate for decision making

3.12 The company presented a partitioned survival model that included 3 main health states: hormone-sensitive disease, hormone-relapsed disease and death. The hormone-sensitive health state included on- and off- treatment

sub-states. The hormone-relapsed health state included 3 sub-states for follow-on treatments. The committee concluded that the model structure was appropriate for decision making.

A scenario analysis using data from ENZAMET to model progression-free survival would be informative

3.13 Both ARCHES and ENZAMET provided data on progression-free survival, but ENZAMET had a longer duration. According to the company, progression-free survival in ARCHES closely resembled that of ENZAMET. Therefore, it used patient-level data from ARCHES to model progression-free survival for enzalutamide plus ADT and ADT alone. It considered that it could not combine data from ENZAMET and ARCHES for progression-free survival because of the different ways in which this outcome was measured. The committee recalled that the definition of progression-free survival in ENZAMET more closely reflected that used in NHS clinical practice (see section 3.8). However, the hazard ratios from both trials were similar (ARCHES: HR 0.39 and ENZAMET: HR 0.34; see section 3.9). As such, the committee considered that using one trial instead of another was unlikely to have had a large effect on the cost-effectiveness results. It concluded that it was reasonable to use data from ARCHES if using data from only a single trial to model progression-free survival.

The company's methods for estimating progression-free survival is not appropriate

3.14 To extrapolate progression-free survival beyond the trial duration and over the lifetime horizon defined in the model, the company used data only from ARCHES (see section 3.13). It fitted a log-normal distribution to both arms of the trial. The committee noted that median follow up in ARCHES was only 14.4 months, and that cancer had not progressed in most people at the final analysis for progression-free survival. This increased the uncertainties associated with estimating average progression-free survival by treatment arm. The immaturity of the data also meant that most

distributions fitted well to the observed trial data. The company based its choice of distribution, the log-normal distribution, on input from clinical experts. It externally validated its choice using data from long-term survival on ADT from STAMPEDE and GETUG. The ERG commented that, when extrapolating progression-free survival using the log-normal distribution, the 5- and 10-year estimates for progression-free survival for ADT seemed implausibly low. The clinical experts considered that around 20% of people who take enzalutamide plus ADT remain progression free at 5 years, which drops to 10% at 10 years. Both values are lower than those suggested in the company's model. The ERG suggested that:

- for ADT alone:
  - the exponential distribution produced estimates for progression-free survival that were more in line with those seen in the UK (based on data from STAMPEDE with a 4-year median follow-up)
- for enzalutamide plus ADT:
  - the log-logistic distribution predicted progression-free survival more in line with the clinical experts' opinion in the shorter term
  - applying the hazard ratio from the network meta-analysis for enzalutamide plus ADT to the extrapolated ADT curve produced estimates more in line with clinical expert expectations for later years.

The committee concluded that, for ADT alone, it preferred using an exponential distribution to extrapolate the data from ARCHES. For enzalutamide plus ADT, it considered that using the hazard ratios from the network meta-analysis produced more plausible estimates than separately fitting a curve to the immature enzalutamide plus ADT data. However, the committee was concerned that this approach implied that the treatment effect would be expected to continue indefinitely, which may not be credible.

The ERG's estimates of survival for people taking enzalutamide plus ADT are more plausible than the company's estimates

3.15 To model overall survival for ADT alone and enzalutamide plus ADT, the company pooled data from ARCHES and ENZAMET (see section 3.9). It extrapolated beyond the trial duration and over the lifetime horizon defined in the model by fitting a Weibull distribution to both arms. The company based its choice of a Weibull distribution on input from clinical experts, and by externally validating its choice using data from STAMPEDE, CHAARTED and GETUG. The ERG considered that the predictions for how long people survive who take ADT alone were reasonably consistent with long-term data from STAMPEDE. However, it was concerned that 10- and 20-year figures reflecting the proportion of people still alive after taking enzalutamide plus ADT were implausibly high with the Weibull distribution. The clinical experts estimated that overall survival with enzalutamide plus ADT would be around 10% to 20% at 10 years, and 0% to 5% at 20 years. The company's modelling suggested that a greater proportion of people would be alive at 20 years than estimated by the clinical experts. The committee noted that, because of the immaturity of the data, most distributions provided similar predictions. Only the Gompertz distribution predicted lower survival for enzalutamide plus ADT than the company's choice. The ERG explained that the Gompertz distribution may have underpredicted survival on enzalutamide plus ADT at later years. The ERG preferred using the hazard ratio from the network meta-analysis applied to the ADT alone curve because it gave better predictions than other curves for enzalutamide plus ADT survival after around 10 years. The committee agreed with the ERG. It concluded that using hazard ratios for enzalutamide plus ADT compared with ADT alone from the network meta-analysis (see section 3.11) estimated the relative treatment effect for enzalutamide plus ADT compared with ADT alone better than the company's approach. This was because it accounted for the different comparators in ARCHES and ENZAMET better than the company's approach of unadjusted pooling.

However, the committee was again concerned that this approach implied that the treatment effect would be expected to continue indefinitely.

It is important to consider the survival advantage scenarios associated with enzalutamide plus ADT compared with docetaxel plus ADT

3.16 To model overall survival with docetaxel plus ADT, the company applied hazard ratios from the network meta-analysis for docetaxel plus ADT compared with ADT alone to the ADT curve. This predicted a survival benefit for docetaxel plus ADT compared with ADT alone, reflecting trial evidence. The company's model also predicted a survival benefit with enzalutamide plus ADT compared with docetaxel plus ADT. The point estimate from the network meta-analysis favoured enzalutamide plus ADT, but the credible interval included 1, the possibility of no effect. The committee noted that people who take enzalutamide plus ADT have fewer life-extending treatment options later (see section 3.4). Therefore, it considered that there might be no survival benefit with enzalutamide plus ADT compared with docetaxel plus ADT. To explore this uncertainty, the ERG provided scenario analyses modelling no survival benefit for enzalutamide plus ADT compared with docetaxel plus ADT. The committee concluded that, given the uncertainty around the overall-survival estimate, it was appropriate to consider these analyses.

Life-extending treatments during hormone-relapsed prostate cancer in ARCHES differ from those used in NHS clinical practice

3.17 The committee acknowledged that people with hormone-sensitive metastatic prostate cancer:

- have enzalutamide plus ADT, docetaxel plus ADT or ADT alone until disease progression
- at progression, have other treatment options
- can have enzalutamide or abiraterone only once
- have fewer options for life-extending follow-on treatments if they have enzalutamide early in the treatment pathway than people who first have

ADT alone or docetaxel plus ADT (see section 3.4).

ARCHES was a double-blind trial, and people could have enzalutamide or abiraterone as follow-on treatments in both treatment arms. At the time of the interim analysis, 54% of people who had follow-on treatments in ARCHES had enzalutamide again or abiraterone after enzalutamide. Also, fewer people in the ADT arm went on to have follow-on treatment with enzalutamide or abiraterone in ARCHES (46%) than modelled by the company (70%). The company did not provide details of treatments during hormone-relapsed prostate cancer in ENZAMET. The committee agreed that the company's modelling of the costs of follow-on treatments reflected NHS costs, but was concerned that the company had not adjusted the effectiveness data to match. In the model, a greater proportion of people having ADT alone incurred costs from having enzalutamide or abiraterone after progression than in ARCHES. However, the company did not account for the benefits of treatment. The committee acknowledged the immaturity of the data from ARCHES, and that the proportion of people on different treatments could change over time. It concluded that it would have preferred the company to adjust for both the costs and effects of treatments for hormone-relapsed metastatic prostate cancer to match NHS practice.

It is uncertain whether the benefits of active treatments persist

3.18 The company's model predicted that the benefit for overall survival with enzalutamide plus ADT compared with ADT alone or docetaxel plus ADT lasted for the model's 30-year time horizon. This was the case whether extrapolated survival curves were used to estimate enzalutamide's treatment effect compared with ADT or the hazard ratio from the network meta-analysis. Data from STAMPEDE showed that there was an initial survival benefit at 5 years with docetaxel plus ADT compared with ADT alone (49% compared with 37%). However, the ERG highlighted that there was no difference in actual overall survival after 8.5 years (23%

compared with 22%). This may have been because people on ADT alone go on to have other life-extending treatments and so 'catch-up' (see sections 3.4 and 3.17). One clinical expert explained that the effect of early systemic treatment lasts for a long time, so catching up might be unlikely. He noted that there were longer follow-up data for abiraterone plus ADT than for enzalutamide plus ADT, and that he thought that both have a similar mechanism of action. These data for abiraterone showed that more people remained alive on abiraterone plus ADT than docetaxel plus ADT or ADT alone beyond 5 years. The ERG presented scenario analyses in which the hazards of survival for enzalutamide plus ADT and the comparators were the same after 8.5 years. The committee concluded that, in the absence of long-term data for enzalutamide plus ADT, the ERG's scenarios in which the hazard ratios were equalised between treatment options after 8.5 years were useful for assessing the uncertainty.

Few people will stop treatment with enzalutamide plus ADT before disease progression

3.19 In the company's model, people could be on or off treatment before disease progression. The ERG was concerned that people who were off treatment before disease progression would maintain the same quality of life as people on treatment, but at no additional cost. In ARCHES, around 12% of people stopped treatment before disease progression. According to the company, only about half of them stopped because of adverse events, while others withdrew consent. The clinical experts explained that, in clinical practice, few people would stop having enzalutamide plus ADT before disease progression because it is generally well tolerated. The committee considered that withdrawing consent is specific to trials and would not be reflected in clinical practice. The ERG noted that, in the company's model, there was a substantial gap between the curves for progression-free survival and time to stopping treatment. The ERG proposed extrapolating the time to stopping treatment using the log-logistic rather than exponential distribution. It considered that this aligned

more closely with the progression-free survival curve. The ERG further noted that, if enzalutamide plus ADT progression-free survival was estimated by applying hazard ratios from the network meta-analysis, the time to stopping treatment could not be modelled separately from progression-free survival. The committee concluded that the time to stopping treatment should have closely resembled progression-free survival. The committee agreed with the ERG using hazard ratios to estimate progression free survival. So, it also concluded that, in this case, progression-free survival should be used to model treatment discontinuation.

Cost-effectiveness estimate

There is a preferred approach to the economic modelling

3.20 The committee's first meeting occurred before the European Medicines Agency (EMA) granted a marketing authorisation. At this point, the committee agreed that its preferred approach to modelling would:

- extrapolate progression-free survival for ADT alone from ARCHES using the exponential distribution (see section 3.14)
- extrapolate overall survival for ADT alone from pooled data using the Weibull distribution (see section 3.15)
- model survival with enzalutamide plus ADT using the hazard ratios from the network meta-analysis applied to the ADT progression-free and overall-survival curves (see sections 3.14 and 3.15)
- model survival with docetaxel plus ADT using the hazard ratios from the network meta-analysis applied to the ADT progression-free and overall-survival curves (see section 3.16)
- adjust the cost-effectiveness estimates for the costs and benefits of treatments used for hormone-resistant metastatic prostate cancer (see section 3.17).

The committee also agreed that it would like to see a scenario in which:

- the hazards of survival are the same at 8.5 years for all comparators (see section 3.18).

The company has updated its commercial offer, which takes into account the preferred approach if possible

3.21 After the committee's first meeting, the appraisal was paused. After the EMA granted a positive opinion, the company updated its commercial offer and acknowledged the committee's preferred assumptions. The committee, in a second closed meeting, considered the ERG's base case, which reflected its preferred assumptions, plus a scenario in which the hazards of survival were the same at 8.5 years for all comparators. The committee was aware that, because of the model the company chose, it adjusted only for costs, and not for the effects of subsequent treatments for hormone-relapsed metastatic prostate cancer to match NHS practice, (see section 3.18).

Enzalutamide plus ADT for hormone-sensitive metastatic prostate cancer is a cost-effective use of NHS resources

3.22 Because of confidential discounts for therapies taken during hormone-relapsed metastatic stage, none of the cost-effectiveness results can be reported here. The ERG presented analyses reflecting the committee's preferred assumptions and scenarios (see section 3.20). In these analyses, the incremental cost-effectiveness ratios were within the range that NICE usually considers an acceptable use of NHS resources (£20,000 to £30,000 per quality-adjusted life year gained). The committee was aware that it had not seen data for people who could take enzalutamide plus ADT, but who could not have docetaxel plus ADT (see section 3.6) and for whom ADT alone is the only NHS treatment option. However, the committee took into account the uncertainties in these people around the relative effectiveness, baseline risk of dying and health-related quality of life. It then concluded that estimates of cost effectiveness were sufficiently low to account for this uncertainty for people who could not have docetaxel plus ADT. The committee therefore

concluded that it could recommend enzalutamide plus ADT for routine commissioning.

Equality issues

The recommendations apply to all people with prostate cancer

3.23 The committee noted that, as in previous appraisals for technologies for treating prostate cancer, its recommendations should apply to transgender women as well as men. No other equality issues were raised during the scoping process or in the submissions for this appraisal.

Innovation

The modelling captures all the benefits

3.24 The company considered enzalutamide to be innovative because it is an oral treatment and needs less monitoring than docetaxel plus ADT. It discussed whether enzalutamide reflects a 'step change' in treatment and whether the model captured the benefits of treatment. The committee recognised that many individuals who have not had enzalutamide plus ADT for hormone-sensitive metastatic prostate cancer have the option of getting it at 2 different points later in the treatment pathway for hormone-relapsed metastatic prostate cancer. It concluded that enzalutamide plus ADT, despite its associated advantages, is not a step change in the treatment of hormone-sensitive metastatic prostate cancer, but that the model captured the relevant benefits.

Other factors

End-of-life criteria are not met

3.25 The company did not make a case for enzalutamide plus ADT meeting NICE's end-of-life criteria. NICE's advice about life-extending treatments for people with a short life expectancy did not apply.

Conclusion

Enzalutamide plus ADT is recommended for hormone-sensitive metastatic prostate cancer

3.26 Early trial results suggested that enzalutamide plus ADT increases progression-free and overall survival compared with ADT alone. Also, the results of an indirect comparison suggested that, compared with docetaxel plus ADT, enzalutamide plus ADT increases progression-free survival but its comparative effect on overall survival is unclear. The cost-effectiveness estimates are below what NICE considers an acceptable use of NHS resources. Therefore, the committee concluded that enzalutamide plus ADT is recommended for hormone-sensitive metastatic prostate cancer.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since

2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has hormone-sensitive metastatic prostate cancer and the doctor responsible for their care thinks that enzalutamide is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
June 2021

6 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.

Verena Wolfram
Technical lead

Emily Leckenby
Technical lead

Ross Dent
Technical adviser

Jeremy Powell
Project manager

Joanne Ekeledo
Project manager

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