NICE National Institute for Health and Care Excellence

NICE guidance

Apalutamide with androgen deprivation therapy for treating high-risk hormone-relapsed non-metastatic prostate cancer

Technology appraisal guidance
Published: 28 October 2021

www.nice.org.uk/guidance/ta740

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Apalutamide plus androgen deprivation therapy (ADT) is recommended, within its marketing authorisation, as an option for treating hormone-relapsed non-metastatic prostate cancer that is at high risk of metastasising in adults. High risk is defined as a blood prostate-specific antigen (PSA) level that has doubled in 10 months or less on continuous ADT. It is recommended only if the company provides apalutamide according to the commercial arrangement.

Why the committee made these recommendations

Hormone-relapsed non-metastatic prostate cancer is usually treated with ADT alone or with darolutamide plus ADT.

Clinical trial evidence suggests that, compared with placebo plus ADT, apalutamide plus ADT increases the time until the disease spreads and how long people live. The cost-effectiveness estimates are within what NICE considers to be an acceptable use of NHS resources. So, apalutamide plus ADT is recommended.

2 Information about apalutamide

Marketing authorisation indication

2.1 Apalutamide (Erleada, Janssen) is indicated 'in adult men for the treatment of non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease'.

Dosage in the marketing authorisation

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

Price

2.3 The price for apalutamide is £2,735 per pack of 112 tablets, each containing 60 mg of the active ingredient (excluding VAT; BNF online, March 2021). The company has a commercial arrangement (simple discount patient access scheme). This makes apalutamide 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 considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

Treatment pathway

Only 1 newer androgen receptor inhibitor would be used in the prostate cancer treatment pathway

3.1 NICE recommends the newer (second-generation) androgen receptor inhibitors enzalutamide plus androgen deprivation therapy (ADT), and darolutamide plus ADT, or abiraterone plus prednisone or prednisolone plus ADT (hereafter abiraterone in combination) for treating hormone-sensitive metastatic or hormone-relapsed non-metastatic prostate cancer at multiple positions in the treatment pathway:

- NICE's technology appraisal guidance on darolutamide with androgen deprivation therapy for treating hormone-relapsed non-metastatic prostate cancer
- NICE's technology appraisal guidance on enzalutamide for treating hormone-sensitive metastatic prostate cancer
- NICE's technology appraisal guidance on enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated
- NICE's technology appraisal guidance on abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated
- NICE's technology appraisal guidance on abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen

- NICE's technology appraisal guidance on enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen.

  People have treatment with a second-generation androgen receptor inhibitor until disease progression, docetaxel for up to 6 cycles, and ADT indefinitely. Apalutamide is another second-generation androgen receptor inhibitor. The Cancer Drugs Fund clinical lead explained that a person will have only 1 of these drugs in the NHS prostate cancer treatment pathway. The clinical experts confirmed that this is because of the similar way the drugs work, and probable resistance to drugs in the same group when used one after another. For example, if prostate cancer metastasises on apalutamide plus ADT, it would be expected to be resistant to subsequent treatment with enzalutamide plus ADT or abiraterone plus ADT. The Cancer Drugs Fund clinical lead confirmed that NHS England would not commission enzalutamide plus ADT or abiraterone plus ADT after apalutamide plus ADT. The committee concluded that in the NHS people with prostate cancer would be offered only 1 newer androgen receptor inhibitor.

Clinical management

People would value additional treatments for hormone-relapsed non-metastatic disease

3.2 Treatment for hormone-relapsed non-metastatic prostate cancer is ADT alone or darolutamide plus ADT. Treatment aims to delay metastasis, which is associated with reduced quality of life and survival. The patient experts explained that anxiety about cancer metastasising causes psychological distress, which adds to debilitating symptoms such as fatigue, pain, and urinary and bowel problems. Apalutamide plus ADT has more than one indication; the one being appraised is for treating hormone-relapsed non-metastatic prostate cancer that is at high risk of metastasising. This is the same indication appraised in NICE's technology appraisal guidance on enzalutamide and darolutamide plus ADT. But, NICE does not recommend enzalutamide for this population, and NICE had not yet recommended darolutamide at the start of this appraisal. So, as per NICE processes, darolutamide plus ADT was not considered a

relevant comparator for decision making. The committee concluded that people with hormone-relapsed non-metastatic prostate cancer would value additional treatment options.

Clinical evidence

The SPARTAN results are in line with planned analyses

3.3 SPARTAN was a phase 3, randomised, multicentre trial comparing apalutamide plus ADT (n=806) with placebo plus ADT (n=401) for hormone-relapsed non-metastatic prostate cancer. The trial population had adenocarcinoma of the prostate that was hormone relapsed and at high risk of metastasis. High risk was defined as a blood prostate-specific antigen (PSA) doubling time of 10 months or less during continuous ADT before randomisation. The committee considered that the participants in SPARTAN reflected people in NHS clinical practice reasonably well. The primary endpoint of SPARTAN was metastases-free survival, that is, the time from randomisation to confirmed evidence of metastasis or death from any cause. The committee appreciated that this reflected progression-free survival, with metastases indicating progression. Secondary endpoints included overall survival. Exploratory endpoints included time to progression-free survival on the first subsequent treatment taken for metastatic disease (PFS2) and health-related quality of life, measured using the EQ-5D questionnaire and the Functional Assessment of Cancer Therapy Prostate Module (FACT-P). PFS2 measures the time from metastasis to the next disease progression on the treatment that people have after the trial treatment. The committee was aware that although PFS2 and EQ-5D were exploratory endpoints, the company used them in its cost-effectiveness modelling. The final analysis for metastases-free survival and an interim analysis for overall survival and PFS2 were done in May 2017. At this time, most people's cancer had metastasised and the metastases-free survival endpoint had been met. In May 2017, the trial was unblinded and people who had placebo plus ADT could cross over to have apalutamide plus ADT if their cancer had not metastasised. The final analyses of overall survival and PFS2 were done in February 2020. After progression to metastatic disease, people could have abiraterone plus prednisone or

prednisolone (from now on referred to as abiraterone in combination) or enzalutamide as subsequent treatment, as well as other treatments (see section 3.1). The committee concluded that the results were in line with the trial's planned analyses.

In SPARTAN, apalutamide plus ADT is clinically effective compared with placebo plus ADT

3.4 In SPARTAN:

- median metastases-free survival for people randomised to apalutamide plus ADT was 40.5 months and for people randomised to placebo plus ADT it was 15.7 months (hazard ratio 0.30, 95% confidence interval [CI] 0.24 to 0.36)
- median overall survival for people randomised to apalutamide plus ADT was 73.9 months and for people randomised to placebo plus ADT it was 59.9 months (hazard ratio 0.78, 95% CI 0.64 to 0.96)
- median PFS2 for people randomised to apalutamide plus ADT was 55.6 months and for people randomised to placebo plus ADT it was 41.2 months (hazard ratio considered academic in confidence by the company so cannot be reported here)
- mean change in EQ-5D-3L visual analogue score showed improvements in the apalutamide plus ADT arm compared with the placebo plus ADT arm at cycles 21 (mean difference 3.03) and 25 (mean difference 3.28), $p<0.05$.

  The committee concluded that apalutamide plus ADT extended metastases-free survival, overall survival, PFS2 and health-related quality of life when compared with placebo plus ADT, and was clinically effective.

The modified RPSFTM is appropriate for decision making, but there is still uncertainty

3.5 The results for overall survival and PFS2 (reported as hazard ratios in SPARTAN) were adjusted to reflect the treatment effect that would be seen in NHS practice. This is because in the trial people randomised to:

- placebo plus ADT crossed over to apalutamide plus ADT

- apalutamide plus ADT went on to have abiraterone plus ADT or enzalutamide plus ADT.

  The committee discussed both situations. In SPARTAN, 76 people (19.0%) randomised to placebo plus ADT crossed over to apalutamide plus ADT. The company explained that this could underestimate the relative benefit of apalutamide plus ADT for overall survival and PFS2. This was because some people progressed or died only after the trial was unblinded (see section 3.3). However, the committee recognised that people with non-metastatic disease in NHS practice who have ADT alone (as in the placebo plus ADT arm of SPARTAN) could have abiraterone in combination or enzalutamide as treatments after their disease had metastasised. This would mean that the trial endpoints may not need to be adjusted if these endpoints occurred after metastasis. The committee also recognised that, in the NHS, people can have only 1 newer androgen receptor inhibitor in the prostate cancer treatment pathway (see section 3.1). Because more people randomised to apalutamide had a second newer androgen receptor inhibitor, the trial results may have overestimated apalutamide plus ADT's apparent effectiveness on PFS2 and overall survival, if having a second newer androgen receptor inhibitor is beneficial. The company considered that the number of people who had a second newer androgen receptor inhibitor is academic in confidence and cannot be reported here. The clinical expert explained that having a second newer androgen receptor inhibitor is unlikely to extend life, but might be associated with adverse effects. The committee appreciated that this type of switching might not bias survival estimates, but it was possible that people could have had a better response to the treatment if they had not had a second newer androgen receptor inhibitor. The company considered several different methods for adjusting. These included the rank preserving structural failure time model (RPSFTM), iterative parameter estimation (IPE), inverse probability of censoring weights (IPCW) and 2-stage estimation. The company chose to use a modified version of the RPSFTM (Diels et al. 2019). The company explained that it did not have enough data to estimate the multiple parameters needed for the RPSFTM and IPE methods, and the IPCW method provided counterintuitive and clinically implausible results. The company also said that the 2-stage method was not viable because of the lack of data and the need for a 'secondary baseline' before changing to apalutamide plus ADT or having a second newer androgen receptor inhibitor. The committee questioned whether it was necessary to adjust the results because of the likely

minimal effect of multiple lines of newer treatments. It appreciated that the modified RPSFTM appeared to be reasonable but it was more like a 2-stage method using aspects of all the adjustment approaches, and propensity weighting. It also considered that the IPCW and 2-stage methods could have been appropriate, if appropriately specified. So, at its first meeting the committee asked that the company explore alternative approaches. At consultation, the company explained that it did not have time to explore alternative approaches. It reiterated its view that the modified RPSFTM was the most appropriate method. The committee was disappointed that the company chose not to explore alternative approaches. But it noted that the adjusted and unadjusted results were similar, which reduced the risks associated with this uncertainty. It concluded that the modified RPSFTM was acceptable for decision making.

Using data from COU-AA-302 to estimate the effect of a second newer androgen receptor inhibitor and to adjust for survival causes uncertainty

3.6 The company manufactures abiraterone as well as apalutamide, and acknowledged that it can access individual patient data from trials of abiraterone in combination for hormone-relapsed metastatic disease. To estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor in SPARTAN using the modified RPSFTM, the company used data from another trial, COU-AA-302, later in the treatment pathway. COU-AA-302 was a randomised trial comparing abiraterone plus prednisone with placebo plus prednisone in people with hormone-relapsed metastatic prostate cancer who had not had cytotoxic chemotherapy. The ERG explained that it could not verify the results of the modified RPSFTM because the company had not provided the requested individual patient data. Although the ERG agreed with using the COU-AA-302 and SPARTAN data, it noted that the survival benefit of abiraterone in combination may be underestimated. This was because people randomised to placebo plus prednisone in the trial could cross over to have abiraterone in combination at unblinding. To address the ERG's concern, the company estimated the survival benefits of abiraterone based on the COU-AA-302 trial's interim and final analysis data. This showed that the final analysis data may be affected by crossover from placebo to abiraterone. For the interim data, the bias

should be small because only 3 people (0.55% of the 542 originally randomised to the placebo plus prednisone arm) had crossed over to abiraterone plus prednisone at this stage. The ERG considered that using the COU-AA-302 interim or final analysis data had a minimal effect on the adjusted hazard ratios for overall survival. It noted that the active treatment in COU-AA-302 had a considerably bigger effect on progression-free survival (used by the company to adjust PFS2) than on overall survival. Therefore, adjusting PFS2 in COU-AA-302 would have a bigger effect on the adjusted hazard ratios and would likely increase the cost-effectiveness estimates. At consultation, the company said that progression-free survival in COU-AA-302 was not affected by crossover from placebo to abiraterone. However, the ERG noted that 17% (93 of 542) of people initially randomised to the placebo plus prednisone arm went on have abiraterone plus prednisone. Because a substantial number of people crossed over, progression-free survival could have been affected by crossover. The company also presented unadjusted results for both crossover and having a second androgen receptor inhibitor, and adjusted results for having a newer androgen receptor inhibitor only. This had a small effect on the results, which the committee noted. It concluded that using COU-AA-302 data to estimate the effect of a second newer androgen receptor inhibitor caused uncertainty, but was unlikely to affect the results much.

Adjusting for the survival benefit of having more than 1 newer androgen receptor inhibitor may be unnecessary

3.7 The committee noted that COU-AA-302 included only people who had never had a newer androgen receptor inhibitor. So, using this data to adjust for the impact of a second newer androgen receptor inhibitor would 'over adjust' the overall survival of people having a second newer androgen receptor inhibitor in SPARTAN. This is because it is unlikely that a second newer androgen receptor inhibitor is as effective as the first one. Because more people in the apalutamide plus ADT arm of SPARTAN had a second newer androgen receptor inhibitor, adjusting for this treatment with COU-AA-302 data could bias against apalutamide plus ADT. The committee agreed that using COU-AA-302 data to estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor caused uncertainty (see section 3.6). It noted that using an

appropriately specified IPCW or 2-stage adjustment method applied to SPARTAN may have avoided the potential bias with estimating the effect of a second newer androgen receptor inhibitor based on data from COU-AA-302. Also, the committee understood that only 1 newer androgen receptor inhibitor would be used in the NHS prostate cancer treatment pathway (see section 3.1). Because they are unlikely to be effective when used again, it may be unnecessary to adjust the SPARTAN survival estimates. The committee agreed that considering a scenario in which people who had a second newer androgen receptor inhibitor survived longer than if they had followed the NHS treatment pathway could be reasonable. However, the committee also recalled the possibility of adverse effects from multiple lines of newer androgen receptor inhibitors. At consultation, the company presented unadjusted results for both crossover and having a second newer androgen receptor inhibitor, and adjusted results for a second newer androgen receptor inhibitor only. This had only a small effect on the results, which the committee noted. The committee concluded that it was uncertain if adjusting for the survival benefit of having a second newer androgen receptor inhibitor was necessary, but the impact of this on results was likely to be limited.

How the company adjusts for crossover in SPARTAN from placebo plus ADT to apalutamide plus ADT may bias results

3.8 The committee considered whether the adjusted or the unadjusted hazard ratios for overall survival and PFS2 were more appropriate for decision making. When adjusting for crossover from the placebo plus ADT arm to the apalutamide plus ADT arm, the company assumed that people had no treatment after placebo plus ADT. But, in clinical practice, people are likely to be offered a newer androgen receptor inhibitor including abiraterone plus ADT or enzalutamide plus ADT as their next treatment. The committee considered that this part of the company's analysis could have biased against placebo plus ADT. It considered that an analysis that did not adjust survival estimates for crossover could be reasonable, if it was assumed that apalutamide has similar effectiveness to abiraterone and enzalutamide. At consultation, the company highlighted that unblinding rather than progression drove crossover in SPARTAN so it considered adjusting to be appropriate. The committee

recognised that adjusting for metastases-free survival could also be appropriate when crossover could occur before metastases. It also considered that, after disease metastasis, treatment with one of these therapies would still be expected in the NHS, making adjustment for overall survival inappropriate. To explore this uncertainty, the company did scenario analyses with and without adjusting for crossover. The committee concluded that it would take these results into account in its decision making.

Both adjusted and unadjusted hazard ratios for overall survival and PFS2 from SPARTAN can be considered for decision making

3.9 The company explained that the adjusted hazard ratio (0.77, 95% CI 0.64 to 0.94) and unadjusted hazard ratio (0.78, 95% CI 0.64 to 0.96) using the modified RPSFTM for overall survival were similar. The adjusted and unadjusted results for PFS2 were also similar to each other. The committee considered that this might be because the company had adjusted both arms of SPARTAN. The company explained that it considered the newer androgen receptor inhibitors the bigger driver of the adjustment results because the benefit of multiple lines of these treatments is small. In their base cases, the company and the ERG used the adjusted hazard ratios for overall survival and PFS2 to adjust for the effect of crossover and having a second androgen receptor inhibitor. Although the difference was minor, the committee took into account both the adjusted and unadjusted hazard ratios for overall survival and PFS2 in its decision making.

SPARTAN is generalisable to NHS practice for people with hormone-relapsed non-metastatic disease

3.10 Unlike in the NHS, people in SPARTAN could have multiple newer androgen receptor inhibitors (see section 3.3). Although the effect of this on overall survival was likely to be minimal, the committee noted that people might have adverse effects (see section 3.5). The committee noted that SPARTAN was a large high-quality trial measuring relevant outcomes. It concluded that, although the treatments people had in SPARTAN did not reflect NHS practice, the trial was otherwise generalisable to NHS practice for people with hormone-relapsed

non-metastatic disease.

Adverse effects

Adverse effects with apalutamide are tolerable

3.11 The clinical experts explained that apalutamide plus ADT is well tolerated. Rash and hypothyroidism have been reported and are manageable. The committee concluded that adverse effects with apalutamide plus ADT are tolerable.

Economic model

The model structure is appropriate for decision making

3.12 To estimate the cost effectiveness of apalutamide plus ADT compared with placebo plus ADT, the company used a partitioned survival model with health states for progression-free survival, progressed disease and death. After disease progression, people could have up to 3 lines of therapy and their health-related quality of life could decline. The company used PFS2 to inform the probability of moving between the first and second treatments for metastatic disease. The company used mean duration in each health state to assign people to the remaining health states. In the progression-free survival health state, people could be on or off treatment as determined by trial data on time to stopping treatment. The company used SPARTAN to estimate efficacy (metastases-free survival and overall survival). The committee concluded that the model structure was appropriate for decision making.

Modelling the SPARTAN data

In SPARTAN, extrapolating metastases-free survival using a Weibull model is uncertain

3.13 Because the decision problem specified a lifetime time horizon

(32 years), the company sought data to estimate what would have happened had the SPARTAN trial lasted longer. The company did not identify any studies that provided longer-term data for metastases-free survival to extrapolate beyond the duration of SPARTAN. It therefore explored a range of curves reflecting hazard functions including generalised gamma and Weibull. Most curves modelling metastases-free survival provided a good fit to the observed data, but the committee recognised the data was of limited duration. The company asked for clinical advice. The advice it received suggested that the Weibull model was the most plausible for both apalutamide plus ADT and placebo plus ADT, although the Weibull function could underestimate metastases-free survival at 10 years for apalutamide plus ADT. The clinical expert at the committee meeting estimated that only 1% to 2% of people having ADT alone as first treatment would be free of metastases at 5 to 10 years, suggesting that the Weibull model was a good fit to the observed data. In its base case, the company used the Weibull model to extrapolate metastases-free survival, and fitted the curves independently to each arm. The ERG also chose the Weibull to model metastases-free survival. However, clinical expert advice to the ERG suggested that none of the models adequately captured metastases-free survival. This was because most curves underestimated the proportion of people who remain metastases free on ADT alone at 5 and 10 years. The exception was the generalised gamma model, which had a clinically implausible long tail to the curve and may overestimate the proportion who remain metastases free on apalutamide plus ADT. The ERG explained that the choice of the model had a large effect on the cost-effectiveness results. It suggested that more flexible models may be appropriate. The committee was aware that metastases-free survival was not adjusted for crossover because this endpoint was reached before people could switch to the other treatment arm (see section 3.3). The committee agreed that, because of the uncertainty associated with the Weibull model, it would have liked to see a more flexible model fitted to extrapolate metastases-free survival beyond the trial duration. At consultation, the company declined to explore flexible approaches. It said that these might be more uncertain than standard parametric models, because of their complexity and number of assumptions. It also said that a flexible approach needed a clinical or statistical reason to justify the time point at which the curves flex, which it considered did not exist. The committee concluded that the

company's approach to extrapolating metastases-free survival was uncertain, which the committee factored into its decision making.

In SPARTAN, extrapolating overall survival using a generalised gamma model is appropriate, but treatment effect beyond the trial is uncertain

3.14 The company used a systematic review (Aly et al. 2018) to identify clinical trial data that it could use to extrapolate overall survival in SPARTAN. It found 3 clinical trials with similar populations to SPARTAN, which it referred to as historical data. But, it did not use this data to extrapolate overall survival because SPARTAN had longer follow up than the historical studies. The company assessed if the proportional hazards assumption held for overall survival. The log-cumulative hazard plot for overall survival in both arms of SPARTAN showed that the curves were relatively parallel over time. The company said that the proportional hazards assumption held based on Schoenfeld residual testing, and the company considered it appropriate to apply jointly fitted models in its original model. That is, rather than fitting survival models to each treatment independently the company fitted 1 survival model to all data, and then generated treatment-specific survival curves by using the treatment group as a covariate. The company chose a Weibull distribution to extrapolate overall survival because of its clinical plausibility. However, the ERG could not verify that proportional hazards would hold in the extrapolated part of the survival curves because of lack of evidence. It noted that the survival estimates from SPARTAN, on which the proportional hazards assumption was tested, were immature. It considered that using models fitted to the treatment arms separately (independently) would be more appropriate. During technical engagement before the first committee meeting, an expert advised the ERG that both Weibull curves were likely underestimated overall survival at 10 years, and possibly at 15 years. The ERG noted that generalised gamma models have a good visual fit to the observed data, and better statistical fits (lower Akaike information criterion or Bayesian information criterion scores) compared with the Weibull models. After technical engagement, both the company and the ERG used the jointly fitted generalised gamma models in their base cases. The committee was aware that the company had adjusted overall survival for crossover and

having a second newer androgen receptor inhibitor. The committee concluded that extrapolating overall survival using the generalised gamma model was appropriate, but the treatment effect beyond the trial was uncertain.

In SPARTAN, extrapolating PFS2 using a Weibull model is appropriate, but estimates are based on immature data

3.15 The company, having assessed that the proportional hazards assumption held for PFS2, applied the Weibull models fitted jointly to both treatments in its base case based on the statistical fits and clinical plausibility. The ERG also jointly fitted Weibull models in its base case, although it noted that the estimates were likely to be uncertain because PFS2 data for apalutamide plus ADT in SPARTAN was relatively immature. The committee concluded that the company and ERG's approach to modelling PFS2 was broadly appropriate but agreed that it was based on immature data.

Treatment effect waning affects the cost-effectiveness results

3.16 The company considered that the benefits of apalutamide plus ADT did not wane over time, so it did not apply any treatment effect waning in its base case. It justified this by noting there was no evidence in SPARTAN that the overall survival curves for both treatments converge over time. The ERG explored treatment effect waning, but considered it unclear from the hazard plots if treatment benefit declined. Because the treatment effect did not wane in abiraterone clinical trials with longer follow up, the ERG's clinical experts did not expect treatment effect waning with apalutamide. However, a study in advanced prostate cancer (Antonarakis et al. 2016) suggested that resistance to newer androgen receptor inhibitors was likely to develop with time. The ERG noted that it was unclear if the study results were generalisable to hormone-relapsed non-metastatic disease. The ERG also noted that resistance to abiraterone or enzalutamide does not necessarily imply that there would be a treatment waning effect for apalutamide. It considered that there was not enough evidence to assess the best approach to estimate the duration of treatment benefits. The Cancer Drugs Fund clinical lead noted that, in practice, most newer hormonal treatments for prostate

cancer lose effectiveness over time. The committee was aware that both the company and the ERG had explored treatment waning in scenarios before technical engagement. The effect on the incremental cost-effectiveness ratio (ICER) was an increase of around £2,000 per quality-adjusted life year (QALY) gained when varying treatment effect waning from 100% to 0% for a duration of 5 years and 10 years. The committee concluded that treatment effect waning affected the cost-effectiveness results.

Treatment costs

The costs of apalutamide are appropriately captured in the model

3.17 The company offered apalutamide to the NHS at a discount, and increased the discount during the appraisal. The committee was aware that duration of treatment determines cost. People have apalutamide plus ADT until disease progression, or until they can no longer tolerate it or choose to stop. The company explained that data reflecting time-to-treatment discontinuation was available from the SPARTAN data cut of February 2020. But, the company chose to model time on treatment using data on time to metastases (metastases-free survival) from an earlier data cut in May 2017. The company explained that it did this because several of the extrapolations for time-to-treatment discontinuation crossed the metastases-free survival curves towards the end of SPARTAN. The committee considered that the best measure of treatment duration was the data measuring time-to-treatment discontinuation. The company explained that the costs used in the model were informed by the minimum of either time-to-treatment discontinuation until progression, or metastases-free survival curves. The company therefore capped the costs. During the first committee meeting, it noted that this might have underestimated the cost of apalutamide in the model. However, at consultation the company stated that it now believed that the costs of treatment had been fully captured. The company also provided a scenario analysis with time on treatment equal to progression-free survival. The ERG confirmed that it agreed with the company's approach in its base case, because no one with progressed disease remains on treatment. The ERG considered the

company's base case would not underestimate the costs of apalutamide. The committee concluded that the costs of apalutamide were appropriately captured in the company's model.

Utility values

The company's utility values are broadly appropriate

3.18 The company assumed that health-related quality of life declines over time because simulated people in the model have disease progression and move onto subsequent lines of therapy (see section 3.12). The company's utility value for having first-line treatment for hormone-relapsed metastatic prostate cancer was from SPARTAN using the EQ-5D-3L. The utility values are considered confidential by the company so cannot be reported here. For second- and third-line treatments for hormone-relapsed metastatic prostate cancer, the company originally used external data from NICE's technology appraisal guidance on abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA387). This was because a limited number of people completed the EQ-5D-3L questionnaire after developing metastases in SPARTAN. The company derived the utility values for second- and third-line treatments from the first treatment by applying a 'relative decline ratio'. It did this by estimating the relative decline in utility in TA387 between first- and second-line treatments for metastatic disease, and first- and third-line treatments for metastatic disease. It then applied these ratios to the progressed utility value from SPARTAN to estimate utilities for second- and third-line hormone-relapsed metastatic prostate cancer. The company also adjusted the derived utility values to account for population differences between SPARTAN and TA387. The company noted that it did this in line with the method described in the NICE Decision Support Unit's technical support document 12 on the use of health state utility values in decision models. The ERG had concerns with the company's adjusted utility values:

- They were much lower than those used in NICE's technology appraisal guidance on enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377) and enzalutamide for hormone-relapsed non-metastatic prostate cancer (TA580). The utility values were 0.658 and 0.612 in TA377 and 0.8 and 0.688 in TA580, for health states reflecting second- and third-line treatments of hormone-relapsed metastatic prostate cancer.

- It was unclear which line of treatment generated the utility values reported in TA387.

- By applying a 'relative decline ratio', the company assumed that the utility values would decrease by the same relative proportion between first- and second-line treatments for hormone-relapsed metastatic prostate cancer (as in TA387). But the committee considered that this assumption may not be appropriate given the different populations in this appraisal (hormone-relapsed non-metastatic disease) and in TA387 (hormone-relapsed metastatic disease before chemotherapy is indicated).

  In its base case, the ERG used the utility values from TA377 without adjusting them. The patient experts reiterated the effect of psychological distress (see section 3.2) and worry about a treatment's loss of efficacy. The clinical expert was aware that EQ-5D, measured in SPARTAN, included questions on anxiety and depression and agreed with the company's utility values. The committee agreed that this disease was associated with a significant effect on quality of life. However, it was concerned with the lack of consistency with utility values used in related technology appraisals. Also, the Cancer Drugs Fund clinical lead explained that the ERG's unadjusted utility values better fitted what had been seen in other disease areas with multiple lines of treatment. Therefore, the committee agreed that, on balance, the ERG's utility values had a higher face validity than the company's adjusted utility values. At consultation, the company updated its base case using unadjusted utility values from TA377 for second- and third-line hormone-relapsed metastatic prostate cancer. The committee concluded that the unadjusted utility values from TA377 were most appropriate for decision making.

End of life

3.19 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company did not make a case for end of life in its submission. The committee concluded that the end of life criteria were not met for apalutamide in hormone-relapsed non-metastatic prostate cancer.

Cost-effectiveness estimates

An acceptable ICER would be in the middle of the range normally considered cost effective, or lower

3.20 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The data is immature for overall survival and PFS2 and the appropriate extrapolation model for metastases-free survival was uncertain. The committee also takes into account other factors, and it was aware that NICE has recommended darolutamide plus ADT for this population (see section 3.22). Therefore, the committee agreed that an acceptable ICER would be in the middle of the range normally considered a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

Apalutamide is cost effective for hormone-relapsed non-metastatic disease

3.21 Because of confidential commercial arrangements for apalutamide and other treatments in the pathway, the cost-effectiveness estimates cannot be reported here. At consultation, the company updated its base case with the committee's preferred assumptions, which were also the ERG's preferred assumptions. These included:

- adjusting for the effect of crossover and having a second androgen receptor inhibitor on overall survival and PFS2 (see section 3.8)

- using unadjusted utility values for second- and third-line hormone-relapsed metastatic prostate cancer (see section 3.18).

At consultation, the company also explored scenarios for some of the uncertainties identified by the committee, including:

- not adjusting treatment effect for either crossover or having a second newer androgen receptor inhibitor
- adjusting treatment effect for a second newer androgen receptor inhibitor only (and not crossover)
- setting time on treatment as equal to progression-free survival (see section 3.17).

The company also presented a probabilistic base-case ICER. It acknowledged that it had chosen not to explore several key uncertainties during consultation. These included exploring methods of adjustment other than the modified RPSFTM, and extrapolating metastases-free survival using a flexible model. The company further increased its discount for apalutamide. The committee considered that the ICER that most closely reflected its preferred assumptions was below the middle of the range of £20,000 to £30,000 per QALY gained. Therefore, apalutamide is recommended as a cost-effective use of NHS resources for treating hormone-relapsed non-metastatic prostate cancer.

Innovation

Apalutamide plus ADT is not innovative for high-risk hormone-relapsed non-metastatic prostate cancer

3.22 Darolutamide, a new androgen receptor inhibitor that was not available when this appraisal started, is now an option with ADT for treating hormone-relapsed non-metastatic prostate cancer at high risk of developing metastatic disease in the NHS. The recommended dose of darolutamide, an oral treatment, is twice daily; the recommended dose of apalutamide is once daily (as 4 tablets). The committee considered this to be an advantage, but not enough to consider apalutamide plus ADT a step-change in treatment and therefore innovative.

Equality issues

The recommendations apply to all people with prostate cancer

3.23 The committee noted that, as in previous NICE technology appraisals of prostate cancer treatments, its recommendations should apply to all people with prostate cancer. It further noted that a person can have a prostate but not identify as a man. Gender reassignment is a protected characteristic under the Equality Act 2010. No other equality issues were raised for hormone-relapsed non-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 prostate cancer and the doctor responsible for their care thinks that apalutamide is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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ISBN: 978-1-4731-4320-3

Accreditation