NICE National Institute for Health and Care Excellence

NICE guidance

Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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 as an option for treating hormone-sensitive metastatic prostate cancer in adults, only if:

- docetaxel is not suitable
- the company provides apalutamide according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with apalutamide plus ADT 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

Hormone-sensitive metastatic prostate cancer is usually treated with docetaxel plus androgen deprivation therapy (ADT), ADT alone or enzalutamide plus ADT. Enzalutamide was not available when this appraisal started.

Clinical trial evidence suggests that, compared with placebo plus ADT, apalutamide plus ADT increases the time until the disease progresses and how long people live.

Apalutamide plus ADT is not cost effective compared with docetaxel. However, compared with ADT, the cost-effectiveness estimates for apalutamide plus ADT are within what NICE considers to be an acceptable use of NHS resources. So, apalutamide plus ADT is recommended for people with hormone-sensitive metastatic prostate cancer only if they cannot have docetaxel.

2 Information about apalutamide

Marketing authorisation indication

2.1 Apalutamide (Erleada, Janssen) is indicated 'in adult men for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy'.

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 or abiraterone after apalutamide. The committee concluded that only 1 newer androgen receptor inhibitor would be used in the treatment pathway for prostate cancer.

Clinical management

People would value additional treatments for hormone-sensitive metastatic disease

3.2 Apalutamide has more than 1 indication for prostate cancer. This appraisal considers apalutamide for treating hormone-sensitive metastatic prostate cancer. Until recently, treatment for hormone-sensitive metastatic prostate cancer included ADT alone, or docetaxel for up to 6 cycles administered as a 1-hour intravenous infusion every 3 weeks, given with ADT and with or without prednisone or prednisolone. People who have had docetaxel plus ADT for hormone-sensitive metastatic disease can have it again if the cancer progresses. NICE now recommends enzalutamide plus ADT for hormone-sensitive metastatic disease. Also, NHS England's interim guidance on treatment options during the COVID-19 pandemic allows use of abiraterone plus prednisone plus ADT but, because of the cost of abiraterone, only for people who cannot tolerate enzalutamide plus ADT. The patient experts explained that people who are diagnosed with metastatic disease may have no or few symptoms and may think that docetaxel worsens quality of life. As a result, some choose to have ADT alone, even though the long-term

outcomes may be worse. The patient experts noted that apalutamide plus ADT is likely to be more effective than ADT alone (see section 3.5) and is generally better tolerated than docetaxel plus ADT (see section 3.3). The committee concluded that people with hormone-sensitive metastatic prostate cancer would value additional treatment options.

Identifying people with hormone-sensitive metastatic disease who cannot have docetaxel involves assessing a person's risks

3.3 For people with hormone-sensitive metastatic prostate cancer, the company proposed apalutamide plus ADT as an alternative to ADT alone or docetaxel plus ADT. This included people who should not have docetaxel because of comorbidities, or who choose not to have docetaxel. The company also proposed a comparison of apalutamide plus ADT with ADT alone for people who could not or should not have docetaxel. The committee noted that defining the group for whom docetaxel is unsuitable was complicated. It had done this in the NICE technology appraisal of abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer with input from the Cancer Drugs Fund clinical lead, clinical experts and stakeholders. The committee was aware that NHS England's clinical commissioning policy statement for docetaxel in combination with ADT defines who may not be well enough to have docetaxel. This includes people with a poor overall performance status (World Health Organization [WHO] performance 3 to 4). 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 to docetaxel. The Cancer Drugs Fund clinical lead had explained during the appraisal of abiraterone that many factors other than performance status may affect whether a person could have docetaxel. The committee noted that people for whom docetaxel is contraindicated or unsuitable would include:

- people for whom docetaxel is contraindicated, as listed in docetaxel's summary of product characteristics and NHS England's clinical commissioning policy statement for docetaxel in combination with ADT
- people with poor performance status (WHO or Eastern Cooperative Oncology Group [ECOG] performance status 3 or 4, and possibly status 2 because

docetaxel is used with caution in this group)

- people with significant comorbidity (for example, cardiovascular, respiratory or liver disease), so prostate cancer is unlikely to be their only life-limiting illness
- people with peripheral sensory neuropathy or poor bone marrow function
- people with poor cognition or social support leading to a decreased ability to understand treatment options or make a decision.

The committee agreed that clinicians should assess the risks and benefits of having docetaxel based on a person's individual risk factors. This should include the advantages and disadvantages of all treatment options, including fewer options for later treatments for people who choose to have apalutamide. The committee appreciated that some people may not be well enough to have docetaxel plus ADT and with or without prednisone or prednisolone, enzalutamide plus ADT, or apalutamide plus ADT, so they would still be offered ADT alone. It concluded that identifying people for whom docetaxel was contraindicated or unsuitable would be based on a clinical framework considering individual patient risk.

Clinical evidence

The TITAN results are in line with planned analyses

3.4 TITAN was a phase 3, randomised, multicentre trial comparing apalutamide plus ADT (n=525) with placebo plus ADT (n=527) for hormone-sensitive metastatic prostate cancer. The trial population had adenocarcinoma of the prostate that had metastasised but was still sensitive to treatment with hormone therapy. The trial included people with ECOG scores of 0, 1 or 2 and excluded people with severe haematological, hepatic or renal dysfunction. The committee considered that the population in TITAN reflected people with hormone-sensitive prostate cancer in NHS clinical practice reasonably well. TITAN's co-primary endpoints were overall survival and radiographic progression-free survival, that is, the time from randomisation to confirmed evidence of radiographic progressive disease or death from any cause. Secondary endpoints included time to cytotoxic chemotherapy. Exploratory

endpoints included progression-free survival on first subsequent treatment (PFS2) and health-related quality of life. The committee was aware that although these were exploratory endpoints, the company used PFS2 and EQ-5D in its cost-effectiveness modelling. Health-related quality of life was measured using the EQ-5D-5L questionnaire, the FACT-P, the Brief Pain Inventory (BPI) and the Brief Pain Inventory Short Form (BPI-SF). The final analysis for radiographic progression-free survival and interim analyses for overall survival and PFS2 were done in November 2018. At this time, most people's cancer had progressed, and the radiographic progression-free survival endpoint had been met. In November 2018, the trial was unblinded and people who had placebo could cross over to have apalutamide plus ADT if their cancer had not progressed. The company did the final analyses of overall survival and PFS2 in September 2020. After disease progression, people could have abiraterone or enzalutamide. The committee was aware that TITAN included people based on whether they could have docetaxel, but only those with an ECOG score of 0 or 1. The company did not present clinical evidence of apalutamide plus ADT's effectiveness compared with ADT alone for people who cannot have docetaxel. The committee concluded that the results were in line with the trial's planned analyses.

Apalutamide plus ADT is clinically effective compared with placebo plus ADT

3.5 In TITAN:

- median radiographic progression-free survival for people randomised to apalutamide plus ADT was not reached and for people randomised to placebo plus ADT it was 22.1 months (hazard ratio 0.5, 95% confidence interval 0.4 to 0.6)
- median overall survival and median PFS2 for people randomised to apalutamide plus ADT and for people randomised to placebo plus ADT are academic-in-confidence and cannot be reported here
- mean change in EQ-5D-5L visual analogue score showed no differences between the apalutamide plus ADT and placebo plus ADT treatment arms for all treatment cycles. For example, mean change at cycle 21 on apalutamide plus ADT was 2.50 and on placebo plus ADT it was 2.04, with a difference of

-0.46 (p=0.7678).

The company used the hazard ratio for the whole population (that is, people with hormone-sensitive metastatic prostate cancer) to show the effectiveness of apalutamide plus ADT for people whom docetaxel is not suitable. The committee understood that no evidence was available for people who cannot have docetaxel as they were likely excluded from the TITAN trial. It considered whether a subgroup of the trial population could be used as a proxy. For example, the patient expert had explained that people who cannot or should not have docetaxel are often older. The company confirmed that it did have a hazard ratio for a subgroup of older people for the endpoint of time to progression or death, but it did not use this. The hazard ratio and upper boundary of the confidence interval crossed 1.0 (no effect) for people 75 years and older, whereas it did not for people younger than 75 years. However, there was no statistically significant difference for interaction. The committee agreed that there would be several uncertainties in using age as a proxy, including confounding factors and because some younger people cannot have docetaxel. At consultation, the company submitted cost-effectiveness analyses for subgroups it considered to represent people who cannot have docetaxel, but no clinical evidence for the subgroup itself (see section 3.28). The committee concluded that apalutamide plus ADT extended radiographic progression-free survival, overall survival and PFS2 when compared with placebo plus ADT. However, there was no clinical evidence for a subgroup who cannot have docetaxel (see section 3.26).

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

3.6 The results for overall survival and PFS2 (reported as hazard ratios in TITAN) 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 TITAN, 208 people (39.5%)

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 3.4). However, the committee recognised that people with metastatic disease who have ADT alone (as in the placebo plus ADT arm of TITAN) could have abiraterone in combination or enzalutamide plus ADT in the NHS (see section 3.9). This would mean that the trial endpoints may not need to be adjusted. The committee also recognised that people can have only 1 newer androgen receptor inhibitor in the NHS prostate cancer treatment pathway (see section 3.1). Because more people randomised to apalutamide plus ADT had a second newer androgen receptor inhibitor, the trial results may have overestimated the effect of apalutamide plus ADT 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 overall survival and PFS2 results. 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 a lack of the 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 (see section 3.12). It appreciated that the modified RPSFTM appeared to be reasonable but 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 suitable, 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

3.7 The company manufactures abiraterone as well as apalutamide, and acknowledged that it can access individual patient data from trials of abiraterone for hormone-relapsed metastatic disease. To estimate and adjust for the survival benefit of a second newer androgen receptor inhibitor in TITAN 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 data, it noted that the survival benefit of abiraterone may be underestimated. This was because people randomised to placebo plus prednisone in the trial could cross over to have abiraterone plus ADT 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 minimally affected 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 to abiraterone, 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

3.8 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 TITAN. 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 TITAN had a second newer androgen receptor inhibitor, adjusting for this treatment with COU-AA-302 data in this way 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 3.7). It noted that using an appropriately specified IPCW or 2-stage adjustment method applied to TITAN 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 TITAN 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 events from multiple lines of newer androgen receptor inhibitors. At consultation, the company presented unadjusted results for both crossing over 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 TITAN from placebo plus ADT to apalutamide plus ADT may bias results

3.9 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 TITAN, so it considered adjusting to be appropriate. The committee recognised that adjusting for radiographic-free survival could be appropriate when crossover occurs before progression. This crossover may have resulted in people randomised to placebo plus ADT having treatment with a newer androgen receptor inhibitor earlier than they would in clinical practice. The committee was aware that treatment with a newer androgen receptor inhibitor would still be expected at some point in the NHS. Therefore, adjustments that imply no such treatment

may be 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 TITAN can be considered for decision making

3.10 The company adjusted for the effect of crossover and of having a second androgen receptor inhibitor in TITAN. In TITAN, some people randomised to placebo plus ADT crossed over to apalutamide plus ADT. The percentage is academic-in-confidence and cannot be reported here. The company explained that most crossover occurred between the interim and final data cuts (see section 3.4). The committee noted that the percentage was high. This meant that adjusting for crossover would likely influence the size of the reported relative efficacy effect between apalutamide plus ADT and placebo plus ADT. In its base case, the company selected the adjusted hazard ratios for overall survival and PFS2. The ERG agreed it was appropriate to adjust the hazard ratios for overall survival and PFS2. The committee concluded that it would take both adjusted and unadjusted hazard ratios for overall survival and PFS2 into account in its decision making.

The company's indirect treatment comparison suggests that apalutamide plus ADT offers an advantage and is well tolerated

3.11 No trial has compared apalutamide plus ADT with docetaxel plus ADT. So, the company indirectly compared apalutamide plus ADT with docetaxel plus ADT, for endpoints including overall survival, radiographic progression-free survival, PFS2 and safety. The network meta-analysis included TITAN and 3 randomised controlled trials linking docetaxel plus ADT to apalutamide plus ADT through the common comparator of placebo plus ADT (CHAARTED, GETUG-AFU15, STAMPEDE). The ERG was broadly satisfied with the company's approach. The results suggested that people having apalutamide plus ADT survive longer than people having placebo plus ADT and people having docetaxel plus ADT. The committee noted that although the hazard ratio was below 1, which indicates a benefit, the confidence interval included the possibility of no

benefit. The results are academic-in-confidence and cannot be presented here. The committee concluded that the company's indirect treatment comparison suggests that apalutamide plus ADT has an advantage over docetaxel plus ADT for efficacy and is well tolerated.

TITAN is generalisable to NHS clinical practice for people with hormone-sensitive metastatic disease

3.12 Unlike in the NHS, people in TITAN, could have additional lines of newer androgen receptor inhibitors, unlike in the NHS. The committee was aware that this may have impacted the treatment effect and caused uncertainty as to what people could have had instead. So, the committee was unclear on the effect of having multiple newer androgen receptor inhibitors on the direction of bias. However, the committee noted that TITAN was a large high-quality trial measuring relevant outcomes. It concluded that TITAN was generalisable to NHS clinical practice.

Adverse effects

Adverse effects with apalutamide are tolerable

3.13 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

3.14 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 TITAN (radiographic progression-free survival and overall survival) to estimate efficacy. The committee concluded that the model structure was appropriate for decision making.

Modelling the TITAN data

In TITAN, extrapolating radiographic progression-free survival using a Weibull model is uncertain

3.15 The company assessed whether the proportional hazards assumption held for radiographic progression-free survival. Based on the log-cumulative hazard plot for radiographic progression-free survival, and a statistical test (Schoenfeld residual testing), it considered that the proportional hazards assumption may be violated. The company, therefore, decided to fit parametric curves to both arms independently. Based on clinical advice, it chose Weibull curves for its base case. The ERG also chose Weibull curves for its base case for both treatments. But the ERG noted that radiographic progression-free survival data for apalutamide plus ADT was highly immature, which is a large driver of the cost-effectiveness results. The ERG also noted that the Weibull models have worse statistical fit (that is, higher Akaike information criterion and Bayesian information criterion scores) than other models. The committee appreciated these measures reflected the model fit, but only to the observed data. Also, expert advice to the ERG suggested that the Weibull models were likely to underestimate the proportion of people who progressed in the ADT arm at 5, 10 and possibly 15 years. Therefore, the ERG suggested that more flexible models may be more appropriate. The committee agreed that, because of the uncertainty with the Weibull model, it would have liked a more flexible model fitted to extrapolate radiographic progression-free survival beyond the duration of TITAN. 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 radiographic progression-free survival was uncertain, which the committee factored into its decision making.

In TITAN, extrapolating overall survival using a Weibull model is acceptable for decision making

3.16 The trial statisticians for TITAN could not estimate the upper boundary of the confidence interval for median overall survival because not enough deaths had occurred. To reduce uncertainty and provide longer follow up, the company reviewed the literature for alternative sources to inform this outcome. It found 7 published trials with ADT arms which had longer follow up than TITAN, and referred to this as 'historical data'. It generated synthetic patient-level data from the published survival curves for the ADT arms of these studies and combined them. The ERG considered this a good attempt to collect longer follow-up data although it noted that the company included only studies published after 2013. The ERG could not verify the company's work because the company did not share its systematic review. The company assumed a common shape between the ADT arm reflecting pooled data, and the placebo plus ADT arm in TITAN. Based on expert opinion, it chose the Weibull curves in its base case because these provided the most clinically plausible extrapolations. Expert advice to the ERG was that survival at 5, 10 and possibly 15 years in both treatment arms was higher in practice than estimated by the Weibull models. Despite this, the ERG chose the Weibull model for its base case because it gave the most conservative estimates. The ERG suggested that more flexible models may be more appropriate. The committee was aware that people have a treatment until disease progression. It noted that the company's model showed that people with hormone-sensitive metastatic disease had similar post-progression survival if they had apalutamide plus ADT or docetaxel plus ADT or ADT alone. The committee questioned whether this had face validity and biological plausibility, because people had fewer post-progression treatment options if they chose to start with apalutamide plus ADT instead of ADT alone or docetaxel plus ADT. The post-progression survival estimates are academic-in-confidence and cannot be reported

here. At consultation, the company found an error made by NICE. The company explained that according to clinical advice, it was both plausible and likely that apalutamide plus ADT would provide a substantial post-progression benefit. However, the company also presented cost-effectiveness results exploring equal post-progression survival between apalutamide plus ADT and its comparators (see section 3.25). The company also explained that it had chosen not to explore flexible survival models (see section 3.15). The committee concluded that, although it would have liked to have seen flexible models explored, the Weibull model was acceptable for decision making.

In TITAN, extrapolating PFS2 is uncertain because it is based on immature data

3.17 The company, having assessed that the proportional hazards assumption holds for PFS2, applied a Weibull model fitted jointly to both treatments in its base case, based on clinical plausibility and consistency (which helps to avoid the issue of curves crossing) with the curves for radiographic progression-free survival (see section 3.15) and overall survival (see section 3.16). The ERG noted that both the Weibull and Gompertz models have the best statistical fits to the observed data. However, the Weibull model likely overestimates PFS2 at 10 and 15 years for people who have apalutamide plus ADT. Also, the ERG stated that the model appears to predict that people spend almost no time on the third-line treatment for metastatic disease. The ERG considered that the Gompertz model was the only clinically relevant alternative, although it is also likely to overestimate long-term survival for people who have apalutamide plus ADT. The ERG noted that, because the PFS2 estimates were immature in TITAN, extrapolating PFS2 assuming proportional hazards was likely to be highly uncertain. For radiographic progression-free survival and overall survival, the ERG suggested that more flexible approaches would be appropriate. The committee concluded that the true estimates of PFS2 after the end of the trial were uncertain because these were based on immature data.

Treatment effect waning affects the cost-effectiveness results

3.18 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 TITAN 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 clinical experts and the ERG 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 resistance to abiraterone or enzalutamide does not necessarily imply that the treatment effect would wane for apalutamide. It considered that there was not enough evidence to assess the best approach to estimate the duration of treatment benefit. 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

3.19 The committee was aware that the company offered apalutamide to the NHS at a discount, which the company increased over the course of 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 took time-to-treatment discontinuation and radiographic progression-free survival from TITAN data cuts that occurred at different times. The company explained that the costs used in the model were informed by the minimum of either time-to-treatment discontinuation, or

radiographic progression-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 should remain 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

3.20 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 3.14). The company's utility value for having first-line treatment for hormone-relapsed metastatic prostate cancer was from TITAN 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 TITAN. 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 TITAN 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 TITAN 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 population in this appraisal (hormone-sensitive 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 highlighted the effect of psychological distress and worry about a treatment's loss of efficacy. The clinical expert was aware that EQ-5D, measured in TITAN, 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.

Modelling the adverse effects of docetaxel

The company and ERG's cost estimates are satisfactory

3.21 In the original model, the company assumed that the adverse effects of docetaxel occurred throughout the hormone-sensitive metastatic prostate cancer pre-progression health state. At technical engagement before the first committee meeting, the ERG explained that this overestimated the costs of managing adverse effects, and it was more appropriate to apply those costs for the first 6 months. The company agreed that this overestimated the costs but suggested that after 6 months of treatment there would be additional costs associated with the adverse effects of ongoing ADT. Therefore, in its base case, the company applied the costs of managing adverse effects for docetaxel for 6 months and the costs of managing adverse effects for ADT alone thereafter. The ERG's base case reflected the company's assumption. The clinical experts explained that the adverse effects of docetaxel were likely to last for 6 to 12 months. The committee concluded that the company and ERG's cost estimates were satisfactory.

The committee is satisfied with the ERG's incidence rates for neutropenia and febrile neutropenia

3.22 The company's model included grade 3 to 4 neutropenia and febrile neutropenia, which are adverse effects associated with docetaxel. In the hormone-sensitive metastatic pre-progression health state, the rates of these adverse effects were based on an epidemiological study on docetaxel use in the NHS (Patrikidou et al. 2017). These were 36.3% for neutropenia and 18.2% for febrile neutropenia per course of 6 cycles of docetaxel. The company suggested that these rates may be low. The ERG noted that the company's sources of observational data had methodological limitations including no information on patient numbers. In its base case, the ERG used pooled data from 3 docetaxel trials (GETUG-AFU15, STAMPEDE and CHAARTED). It estimated combined

rates of 10.6% for febrile neutropenia and 15.4% for neutropenia, at a constant rate over 6 months. STAMPEDE included only people from the UK and Switzerland, and was therefore more likely to represent NHS clinical practice. At consultation, the company also applied the ERG's approach to these incidence rates. The committee concluded that it was satisfied with the company and the ERG's pooled incidence rates for neutropenia and febrile neutropenia.

End of life

3.23 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-sensitive metastatic prostate cancer.

Cost-effectiveness estimates

An acceptable ICER would be lower than the middle of the range normally considered cost effective

3.24 The committee recalled its earlier conclusion that the data is immature for overall survival and PFS2 and there is uncertainty about the appropriate extrapolation model for radiographic progression-free survival, overall survival and PFS2. So, the committee agreed that an acceptable ICER would be lower than 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 not cost effective in the whole population for hormone-sensitive metastatic disease

3.25 Because of confidential commercial arrangements for apalutamide and subsequent treatments, the cost-effectiveness estimates cannot be reported here. The committee was satisfied with some of the ERG's

preferred assumptions. These included:

- not adjusting treatment effect for either crossover or having a second androgen receptor inhibitor on overall survival and PFS2 (see section 3.7)
- using unadjusted utility values for second- and third-line metastatic disease (see section 3.20)
- using pooled incidence rates for neutropenia (15.4%) and febrile neutropenia (10.6%; see section 3.22)
- incremental cost-effectiveness analyses including docetaxel plus ADT, apalutamide plus ADT, and ADT alone.

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

- not adjusting treatment effect for both crossover and having a second newer androgen receptor inhibitor
- adjusting treatment effect for having a second newer androgen receptor inhibitor (and not crossover)
- setting time on treatment equal to progression-free survival (see section 3.19)
- setting equal post-progression survival between intervention and comparator arms (see section 3.16).

The company also presented probabilistic ICERs. The company increased its confidential discount for apalutamide. Based on incremental deterministic ICERs, the committee agreed that the cost-effectiveness estimates for apalutamide plus ADT compared with docetaxel plus ADT were well above the range normally considered a cost-effective use of NHS resources. So, it concluded that apalutamide could not be recommended as a cost-effective use of NHS resources for treating hormone-sensitive metastatic prostate cancer.

The committee considered a group of people who cannot have docetaxel, but the lack of direct evidence increases uncertainty

3.26 The committee considered whether there was a group of people for whom apalutamide plus ADT would be a clinically and cost-effective option. It considered the population who cannot have docetaxel, having discussed how to identify them (see section 3.3). The committee was aware that docetaxel was not a relevant comparator for them or a treatment they would have when their disease became resistant to hormone treatment. The relevant comparator was ADT alone. The committee was aware that it had no direct relevant evidence with which to consider the cost effectiveness of apalutamide plus ADT compared with ADT alone for people who cannot have docetaxel. The committee was aware that TITAN excluded people who would be most likely not to be able to have docetaxel in NHS practice, for example people with an ECOG score of 2 or more (see section 3.4). So, the committee looked at evidence of effectiveness for people who had risk factors, such as age, that would make them more likely to be unsuitable for docetaxel. The committee was aware of data from stakeholders and NHS England documenting the association between older age and decreasing use of docetaxel for hormone-sensitive disease. It was also aware of subgroup analyses from TITAN which showed a hazard ratio for progression or death of 0.65 for people over 75 years compared with hazard ratios of 0.45 and 0.47 for younger age groups. The committee was aware that there was no evidence of treatment-by-age interaction which meant that if there is an interaction, the analysis did not find it.

3.27 After consultation, for the committee's third meeting, the company did analyses for groups it considered to represent people who cannot have docetaxel. These included people:

- with low volume disease (the company considered chemotherapy to be less effective for this group, but did not provide evidence)
- with an ECOG score of 1 (representing a more unwell population than an ECOG score of 0)
- over 75 years.

It also included scenarios:

- reducing utility values for all lines of treatment by 10% (to explore utility values reflecting the older more unwell population)
- removing chemotherapy during metastatic hormone-relapsed disease (to explore a model in which people do not go on to get docetaxel or chabazite when their disease becomes hormone relapsed).

3.28 The committee questioned the relevance of the company's response defining people with low volume disease or people with an ECOG score of 1 as people who cannot or should have docetaxel. The Cancer Drugs Fund clinical lead explained that low volume disease was not a proxy for not being able to have docetaxel. The committee noted that an ECOG score of 1 represented a relatively well population. It recalled that the STAMPEDE trial of docetaxel plus ADT plus prednisone enrolled people with an ECOG score of 0, 1 and 2 and showed that docetaxel was equally effective in people with a score of 0 and a score of 1 and above. Moreover, in the NHS, people with an ECOG score of 1 would likely be offered chemotherapy. The committee concluded that the company's analyses did not reflect a group who could not have docetaxel. Although older people are less likely to be able to have docetaxel, some younger people cannot have docetaxel, and the committee would be unlikely to make age-based recommendations. The committee concluded that, in the absence of evidence directly addressing the population of interest, this increased the uncertainty in the cost effectiveness results. When taking into account the company's increased discount and the uncertainty, the committee considered that the ICER most closely reflecting its preferred assumptions is within a cost-effective use of NHS resources. So, the committee recommended apalutamide plus ADT as an effective use of NHS resources for treating hormone-sensitive metastatic prostate cancer for people who cannot have docetaxel.

Innovation

Apalutamide plus ADT is not innovative for hormone-sensitive metastatic prostate cancer

3.29 The company considered apalutamide plus ADT to be innovative because it is an oral treatment and requires less monitoring than docetaxel plus ADT. However, the committee noted that enzalutamide, a new oral androgen receptor inhibitor that was not available when this appraisal started, is now an option with ADT for treating hormone-sensitive metastatic prostate cancer in the NHS. It concluded that apalutamide plus ADT was not innovative.

Equality issues

The recommendations apply to all people with prostate cancer

3.30 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. The committee also noted that, in clinical practice, older people are less likely to have docetaxel than younger people. It was aware that although docetaxel is more likely to be contraindicated or unsuitable for older people, age alone will not determine whether a person could or should have docetaxel in clinical practice. The committee was also aware that making recommendations by age to reflect people who cannot have docetaxel could discriminate against younger people for whom docetaxel is contraindicated or unsuitable. The committee concluded that, by considering the cost effectiveness for people who could not have docetaxel (see sections 3.26 to 3.28), it took into account older people in its recommendations.

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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