NICE National Institute for Health and Care Excellence

NICE guidance

Darolutamide with androgen deprivation therapy and docetaxel 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 Darolutamide with docetaxel is recommended, within its marketing authorisation, as an option for treating hormone-sensitive metastatic prostate cancer in adults. Darolutamide is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Usual treatment for hormone-sensitive metastatic prostate cancer always includes androgen deprivation therapy (ADT), which may be given alone, or with docetaxel or enzalutamide. Darolutamide plus ADT and docetaxel would be another treatment option.

Clinical trial evidence shows that, compared with taking placebo plus ADT and docetaxel, people taking darolutamide plus ADT and docetaxel live longer, and have longer before their cancer gets worse or stops responding to ADT. There is also an indirect comparison comparing darolutamide plus ADT and docetaxel with usual treatment. The results suggest that darolutamide increases how long people live, and how long they have before their cancer gets worse or stops responding to ADT.

The cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. So, darolutamide is recommended.

2 Information about darolutamide

Marketing authorisation indication

2.1 Darolutamide (Nubeqa, Bayer) is indicated for 'the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of darolutamide is £4,040.00 for a 28-day supply of 112 tablets, each containing 300 mg (excluding VAT, BNF online accessed March 2023).

2.4 The company has a commercial arrangement. This makes darolutamide 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 evaluation committee considered evidence submitted by Bayer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Need for treatment options

3.1 The patient and clinical experts would welcome an additional treatment option for hormone-sensitive metastatic prostate cancer. The patient experts stated that an increasing number of people have metastatic prostate cancer at the initial diagnosis, which is associated with a worse prognosis. They also stated that the approach of adding darolutamide to ADT and docetaxel is new and innovative in prostate cancer. They added that many younger people with hormone-sensitive metastatic prostate cancer would be willing to have darolutamide plus ADT and docetaxel if it meant that they have more years of life in better health. A patient expert explained that, apart from feeling weak for a few days after each docetaxel dose, darolutamide plus ADT and docetaxel was well tolerated and did not otherwise affect usual daily activities. A clinical expert explained that darolutamide plus ADT and docetaxel will be beneficial across the whole patient population. They noted the importance of this treatment for people of Black, African and Caribbean family backgrounds. This was because, depending on the geographical region, there may be more people from these backgrounds, who may have more aggressive disease and so may benefit more. The committee concluded that darolutamide plus ADT and docetaxel would be an important treatment option for people with hormone-sensitive metastatic prostate cancer.

Clinical management

Treatment pathway

3.2 The company positioned darolutamide plus ADT and docetaxel in the hormone-sensitive metastatic part of the prostate cancer pathway, where the treatment options include:

- ADT alone (see NICE's guideline on prostate cancer)
- docetaxel with ADT (see NICE's guideline on prostate cancer)
- enzalutamide with ADT (see NICE's technology appraisal guidance on enzalutamide for treating hormone-sensitive metastatic prostate cancer)
- apalutamide with ADT when docetaxel is unsuitable (see NICE's technology appraisal guidance on apalutamide with ADT for treating hormone-sensitive metastatic prostate cancer).

The clinical experts agreed with the treatment options and the positioning of darolutamide plus ADT and docetaxel in the treatment pathway for people with hormone-sensitive metastatic prostate cancer. A clinical expert noted that having darolutamide plus ADT and docetaxel in the hormone-sensitive metastatic stage limits treatment options in the hormone-relapsed metastatic stage. This is because an anti-androgen (apalutamide, darolutamide or enzalutamide) would have already been used in the hormone-sensitive metastatic stage, and NHS practice is to only use an anti-androgen once in the treatment pathway. The clinical expert noted that more people are expected to have an anti-androgen in the hormone-sensitive metastatic stage than in the hormone-relapsed metastatic stage. The clinical expert estimated that between 10% to 15% of people have ADT with docetaxel in the hormone-sensitive metastatic stage. The clinical experts explained that some younger people with hormone-sensitive metastatic prostate cancer may prefer to have ADT with docetaxel rather than an anti-androgen (enzalutamide) because treatment is shorter, unlike the more prolonged treatment with an anti-androgen. Some reasons people may not have enzalutamide are contraindications, drug–drug interactions, epilepsy, or intolerance to or toxicity of an anti-androgen. A clinical expert added that improved progression-free survival is valuable to people because of the difficult consequences of

progression to the hormone-relapsed disease stage. NHS England's clinical lead for the Cancer Drugs Fund stated that in national clinical practice, 50% of anti-androgen use is in the hormone-sensitive setting, and 50% is in the hormone-relapsed setting. In addition, 85% to 90% of people having enzalutamide are eligible to have chemotherapy, but around 1.0% to 1.5% of people have chemotherapy followed by ADT with enzalutamide. The clinical expert explained that 50% of people having an anti-androgen in the hormone-relapsed setting is a legacy effect of introducing anti-androgens earlier in the treatment pathway during COVID, so is expected to decrease over time, in addition to general changes to the treatment pathway over time. The committee concluded that darolutamide plus ADT and docetaxel is positioned appropriately in the treatment pathway.

Comparators

3.3 The NICE scope for this evaluation lists ADT alone, ADT with docetaxel, and ADT with enzalutamide as comparators for darolutamide plus ADT and docetaxel. The clinical experts agreed with the company and EAG that monotherapy with bicalutamide (a standard non-steroidal anti-androgen, a component of ADT) is not a relevant comparator because it is not used in standard care. Additionally, apalutamide with ADT is not a relevant comparator because it is only recommended by NICE as an option for treating hormone-sensitive metastatic prostate cancer if docetaxel is not suitable. Abiraterone with ADT is not a relevant comparator because it is not recommended by NICE. The committee concluded that ADT alone, ADT with docetaxel, and ADT with enzalutamide are all relevant comparators, but that most people have ADT with enzalutamide (see section 3.2).

Subgroups

3.4 The NICE scope included high-risk and newly diagnosed metastatic prostate cancer as subgroups. But the company noted that these definitions were used inconsistently in the hormone-sensitive metastatic prostate cancer trials. After technical engagement, the company presented comparative efficacy estimates for overall survival and time to 'castration-resistant prostate cancer or death' (CROD), representing progression-free survival, for darolutamide plus ADT and docetaxel

compared with placebo plus ADT and docetaxel, for:

- the intention-to-treat population
- the population with metastatic disease at diagnosis
- the population with high-risk disease.

The effectiveness of darolutamide was similar across the intention-to-treat population and subgroups. But the subgroups were not included in the network meta-analysis (see section 3.8) or model (see section 3.12) because of limited data and inconsistencies across the network. The EAG agreed with the company's reasoning. The clinical experts explained that a different benefit would not be expected for the different subgroups. The committee concluded that it was appropriate to consider the effectiveness of darolutamide plus ADT and docetaxel for the whole marketing authorisation population.

Clinical evidence

ARASENS trial generalisability

3.5 The clinical-effectiveness evidence for darolutamide plus ADT and docetaxel compared with ADT and docetaxel was from the ARASENS trial. This was an international, phase 3, double-blind, placebo-controlled, randomised controlled trial in metastatic hormone-sensitive prostate cancer. It compared darolutamide plus ADT and docetaxel, and placebo plus ADT and docetaxel. There were 1,306 adults enrolled in the intention-to-treat population, and 29 of these were from the UK across 8 centres. The trial grouped people according to:

- extent of disease
- alkaline phosphatase level.

The ARASENS trial design included an active follow up, in which assessments were done every 12 weeks for up to 1 year, and a long-term survival follow up, in which assessments were done until the end of the study. After treatment was stopped, people could either end the study with no follow up, enter the

active follow up and subsequently the long-term survival follow up, or enter directly from stopping treatment to the long-term survival follow up. The EAG noted that most people in the trial had metastatic disease at baseline diagnosis. The clinical experts agreed that the high percentage of people with metastatic disease at diagnosis was generalisable to the NHS population in which double or triple treatment regimens such as darolutamide would be considered. They noted that the proportion of people with metastatic disease at diagnosis was consistent with other trials in hormone-sensitive metastatic prostate cancer (ARCHES and TITAN). The EAG also noted that most of the people in the trial had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0, which is associated with better prognosis and outcomes, but at the same time, most people in the trial had metastatic disease at diagnosis, which is associated with worse prognosis and outcomes than hormone-sensitive metastatic prostate cancer that has progressed after localised disease. The clinical experts explained high numbers of people with an ECOG PS score of 0 in the trial was expected, because a clinical judgement is made to ensure chemotherapy is safe and appropriate. The EAG noted that there were fewer people of Black or African American family background (who tend to have worse outcomes, see section 3.1) in the trial than in NHS clinical practice. The clinical experts explained that the demographics are applicable to the overall NHS population, but noted that some geographical areas where there are more diverse populations may be under-represented. The committee concluded that overall, ARASENS is generalisable to NHS clinical practice.

Clinical effectiveness

Overall survival benefit with darolutamide

3.6 The primary outcome in ARASENS was overall survival. The company presented results that showed a treatment benefit of darolutamide compared with placebo (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.57 to 0.80). The company did not adjust the overall survival results for subsequent treatments with a second anti-androgen, which was possible in the ARASENS trial but not in clinical practice. But the EAG and clinical experts agreed that a second anti-androgen is unlikely to have a clinical benefit. The committee noted that overall survival results from ARASENS suggests a treatment benefit of darolutamide plus ADT and

docetaxel compared with placebo plus ADT and docetaxel.

Time to CROD as a proxy for progression-free survival

3.7 Progression-free survival was measured through the composite outcome time to CROD. There was a treatment benefit of darolutamide compared with placebo (the company considers the exact numbers to be confidential, so they cannot be reported here). Time to CROD was defined as the time from randomisation to a 'castration-resistant prostate cancer event' (either radiological, or biochemical with prostate-specific antigen progression) or death. This outcome was used as a proxy for progression-free survival in the economic model (see section 3.12). Time to developing hormone-relapsed prostate cancer (a synonym for castration-resistant prostate cancer) was a secondary endpoint in the ARASENS trial. The company explained that this better reflects clinical practice than radiographic progression-free survival, which is measured on a fixed schedule. Imaging for time to developing hormone-relapsed prostate cancer was done yearly after the end of docetaxel treatment, or at the investigator's discretion in response to clinical factors (for example, prostate-specific antigen progression, symptomatic progressive disease, or a change of antineoplastic therapy). The EAG agreed that time to developing hormone-relapsed prostate cancer was an appropriate outcome, and time to CROD was an appropriate proxy for progression-free survival in the model. The clinical experts explained that time to CROD may be more clinically relevant, because imaging was done based on clinically relevant events such as increasing prostate-specific antigen levels, rather than at set intervals for radiological progression-free survival, so it may be possible to detect progression earlier. The committee noted that it was important to consider how similar or different time to CROD was to radiological progression-free survival, but the company did not have any data on this comparison because ARASENS was not designed to measure radiological progression-free survival at set intervals. The committee acknowledged the heterogeneity in the definitions of progression-free survival across studies of hormone-sensitive metastatic prostate cancer. It agreed that time to CROD was an appropriate outcome to use for decision making, and that the results suggested a treatment benefit of darolutamide plus ADT and docetaxel compared with placebo plus ADT and docetaxel.

Indirect treatment comparison

Studies included in the network meta-analysis

3.8 The company's network meta-analysis indirectly compared darolutamide plus ADT and docetaxel with its comparators (see section 3.3). It included 6 trials and produced a network of:

- darolutamide plus ADT and docetaxel compared with placebo plus ADT and docetaxel (ARASENS)
- enzalutamide plus ADT compared with ADT alone (ARCHES)
- docetaxel plus ADT compared with ADT alone (CHAARTED; GETUG-AFU15)
- abiraterone plus prednisolone and ADT compared with ADT alone (LATITUDE; STAMPEDE-2)
- docetaxel plus ADT compared with ADT alone (STAMPEDE-3)
- abiraterone plus ADT compared with ADT alone (STAMPEDE-4).

Although abiraterone was not a relevant comparator (because is not recommended by NICE), it provided a source of indirect evidence. The company did not find any statistically significant inconsistencies between the direct and indirect evidence in the network. The EAG's scenario analysis removed abiraterone from the network meta-analysis and assumed STAMPEDE-4 was a subset of STAMPEDE-2 and STAMPEDE-3, rather than separate trials, because the populations may have overlapped. The committee considered it appropriate to explore the impact on the cost effectiveness of removing abiraterone from the network. A further analysis by the EAG on the individual residual deviance for each trial in the network suggested that STAMPEDE-4 contributed more to the total residual deviance than the other trials, and that there was inconsistency in the network. The committee noted that the definitions of progression-free survival used across the trials differed. The base-case network meta-analysis used time to CROD (ARASENS), and the closest matching definitions from the other trials (time to clinical progression [CHAARTRED], radiological progression-free survival [ARCHES, GETUG-AFU15, LATITUDE], and failure-free survival [STAMPEDE-2, STAMPEDE-3,

STAMPEDE-4]) were used. The company also did an alternative network meta-analysis, in which the progression-free survival definition did not need to include death. This was to explore the uncertainty of the different progression-free survival definitions. Here, time to developing hormone-relapsed prostate cancer was used as a measure for progression-free survival in ARASENS, and the closest matching definition was used from the other trials. The company stated that using the alternative definition of progression had only a limited impact on the results. In terms of baseline characteristics across the populations included in the trials, 17.8% of people in the ARCHES trial had had docetaxel previously. But the company used the hazard ratio for the overall population because it was similar to that of the group who did not have previous docetaxel. Comparing the baseline characteristics across the studies included in the network suggested similarities across the trials in terms of age, ECOG PS score, Gleason score and prostate-specific antigen level. But there were proportionally more people with stage 4 prostate cancer in ARASENS than in the other trials. The company's subgroup analysis using data from ARASENS did not show that age, ECOG PS score, Gleason score, prostate-specific antigen level or prostate cancer stage were treatment-effect modifiers for overall survival because they had overlapping confidence intervals. The committee acknowledged that subgroup analyses would be unlikely to be appropriately powered to detect differences in potential treatment-effect modifiers. But it concluded that the studies included in the company's network meta-analysis were appropriate for decision making, but there was uncertainty about the consistency between the direct and indirect evidence included.

Types of network meta-analysis

3.9 In its base case, the company used a fixed-effects network meta-analysis, assuming no heterogeneity between studies, to model overall survival. The fixed-effects network meta-analysis for overall survival had a lower deviance information criterion score than the random-effects model, indicating a better model fit. The company used a random-effects network meta-analysis for progression-free survival because of potential heterogeneity from the different outcome definitions used across the studies (see section 3.8). The random-effects network meta-analysis for progression-free survival had a lower deviance information criterion score than the fixed-effects model, indicating a better model fit. The committee concluded that the network meta-analysis was appropriate

for decision making.

Treatment switching in the network meta-analysis

3.10 The ARCHES and LATITUDE trials in the network meta-analysis allowed treatment switching after the primary data analysis and unblinding. In the ARCHES trial, treatment switching from placebo to the intervention arm was 31%, and in the LATITUDE trials it was 12%. The company did not adjust for treatment switching. It considered that adjusted hazard ratios may not reflect clinical practice because they would assume people in the control arm did not subsequently have an anti-androgen. But unadjusted hazard ratios may not reflect clinical practice if people have an anti-androgen earlier than they would in clinical practice, because treatment switching was after unblinding rather than disease progression. The EAG did a scenario analysis that adjusted the hazard ratios for treatment switching. This suggested an improved treatment effect for enzalutamide (ARCHES) and abiraterone (LATITUDE) compared with darolutamide plus ADT and docetaxel (the exact numbers are confidential and cannot be reported here). The EAG noted that because there was treatment switching in the comparator trials, using unadjusted hazard ratios may mean that the relative treatment effect of darolutamide plus ADT and docetaxel was overestimated. So, it suggested that separately adjusting for treatment switching in ARCHES and LATITUDE may be appropriate. The company argued that adjusted hazard ratios may underestimate the treatment efficacy of darolutamide, because after adjustment, the proportion of subsequent treatment with a first anti-androgen was disproportionally greater in ARASENS compared with the unadjusted hazard ratios. This would favour the comparators (enzalutamide and abiraterone) because of a greater impact on survival for the placebo arm from having a first anti-androgen. The committee acknowledged that using unadjusted hazard ratios may better reflect clinical practice because people in the placebo arm would subsequently have a first anti-androgen, and a second anti-androgen is not likely to add clinical benefit. The committee concluded that unadjusted hazard ratios may better reflect clinical practice, and so would be appropriate to use in the model.

Progression-free survival estimates for comparators in the

network meta-analysis

3.11 The latest progression-free survival estimates from ARCHES and STAMPEDE-2 were not available for the company's original submission. At technical engagement the company updated its network meta-analysis with the most recent radiological progression-free survival estimates from ARCHES and failure-free survival estimates from STAMPEDE-2, and applied these to progression-free survival and time-on-treatment because the hazard ratios in the model were interdependent. It noted that the updated results from ARCHES were consistent with overall survival in the network meta-analysis, and it closely matched the ARASENS follow up. The EAG did not use the updated progression-free survival estimates in its base case because of unexplained notable differences in the hazard ratios (HR 0.63 [95% CI 0.52 to 0.76]) compared with the original estimate (HR 0.39 [95% CI 0.30 to 0.50]). It noted that the original radiological progression-free survival estimate from ARCHES used centralised independent review, whereas the updated radiological progression-free survival estimate used investigator assessment. The EAG added that the difference in assessment method may explain the difference in hazard ratios, but that the centralised assessment is usually conservative. A clinical expert said that a greater treatment effect using centralised assessments was plausible because it was driven by meeting the Response Evaluation Criteria In Solid Tumours (RECIST) criteria, so people would be more likely to continue the trial treatment. A clinical expert added that conventional imaging (that is, CT or bone scans) tend to show progression later than indicators such as prostate-specific antigen levels. The clinical experts explained that individual investigator assessments reflect decision making in NHS clinical practice. But it was unclear to the committee whether the investigators were blinded for either the centralised assessment or investigator assessment. On balance, the committee noted a general preference for more mature data, where available, and it preferred to use the latest progression-free survival estimates from ARCHES and STAMPEDE-2.

Economic model

Company model

3.12 In its submission, the company presented a 3-state partitioned survival model to estimate the cost effectiveness of darolutamide plus ADT and docetaxel compared with enzalutamide plus ADT, ADT plus docetaxel, and ADT alone, for adults with hormone-sensitive metastatic prostate cancer who can have chemotherapy. The 3 health states were pre-progression (hormone-sensitive metastatic prostate cancer), post-progression (hormone-relapsed metastatic prostate cancer), and death. In the pre-progression health state, people could be on or off treatment (ADT only), and post-progression, people could have up to 3 lines of treatment. Darolutamide and enzalutamide continued until disease progression or unacceptable toxicity; docetaxel continued for 6 cycles; and ADT continued indefinitely as a background therapy. The model cycle was 28 days, with a half-cycle correction, and had a 34-year lifetime time horizon. Overall survival and time to CROD from the ARASENS trial were included in the network meta-analysis. The efficacy of darolutamide plus ADT and docetaxel, and the comparator treatments (enzalutamide with ADT, and ADT alone) were derived by applying the network meta-analysis hazard ratios to extrapolated docetaxel data. The efficacy of docetaxel with ADT was from ARASENS. The committee noted that the quality-adjusted life years (QALYs) were accrued from people living longer, with a better quality of life from delayed progression to the hormone-relapsed metastatic prostate cancer state. The committee concluded that the model was suitable for decision making.

Overall survival and progression-free survival extrapolations

3.13 In its original submission, the company modelled overall survival using a log-normal distribution. It compared the extrapolations to the CHAARTED and STAMPEDE-3 (considered more representative of NHS clinical practice) survival estimates over 9 years for docetaxel. After technical engagement, the company aligned with the EAG's preference of using a log-logistic distribution. This was because clinical advice to the EAG suggested that the overall survival estimates for darolutamide over

30 years were optimistic. The log-logistic distribution fitted the observed overall survival data from ARASENS and STAMPEDE-3 and was more conservative than the log-normal distribution. The company modelled time to CROD using the generalised gamma distribution in its original submission, but after technical engagement, updated this to align with the EAG's choice of the log-normal distribution to account for potential optimistic predictions. The committee had concerns about the clinical plausibility of the overall and progression-free survival estimates for darolutamide plus ADT and docetaxel and its comparators extrapolated over 30 years. After the committee meeting, the clinical experts agreed that for overall survival and time to CROD, the estimates up to 10 years were consistent with evidence from the STAMPEDE-3 trial. Beyond this, the progression-free survival estimates were above the level expected in clinical practice. The clinical experts added that it is unlikely that people would be progression free over 20 and 30 years. For the time-on-treatment extrapolation, the clinical experts agreed more people were on treatment at 20 years than would be expected in clinical practice. The committee concluded that the optimistic extrapolations for darolutamide and the comparators added to the uncertainties.

Health-related quality of life

Docetaxel disutility

3.14 The ARASENS trial did not collect EQ-5D data, so the company used the EAG's preferred utilities from NICE's technology appraisal guidance on enzalutamide. These utilities were from the ARCHES and AFFIRM trials and included all the relevant comparators for darolutamide plus ADT and docetaxel. The EAG preferred to add a 0.02 disutility for docetaxel use for 6 months. This was in line with NICE's technology appraisal guidance on apalutamide, in which a 0.02 disutility was added for 12 months, because a generally lower health-related quality of life is expected. After technical engagement, the company used a 0.02 disutility for docetaxel for 6 months, and also adjusted the disutility to account for the proportion of people alive during the 6 months. The EAG noted that the company's additional adjustment had a negligible impact on the cost-effectiveness estimates. The committee concluded that the utility values

used by the company and EAG were appropriate for decision making.

Treatment-effect waning

Darolutamide plus ADT and docetaxel treatment effect over time

3.15 The committee wanted to explore whether, on a population level, the benefit of treatment with darolutamide is likely to stay the same or change over time. The company did not explore treatment-effect waning for darolutamide plus ADT and docetaxel, but previous NICE technology appraisal guidance explored treatment-effect waning in scenarios (NICE's technology appraisal guidance on abiraterone for treating newly diagnosed high-risk hormone-sensitive metastatic prostate cancer, apalutamide and enzalutamide). The clinical experts questioned the clinical plausibility of treatment-effect waning and noted that because ARASENS was a more mature trial with longer follow up, and the comparator included docetaxel, minimal treatment-effect waning would be expected. The clinical lead for the Cancer Drugs Fund highlighted that, because darolutamide is continued until disease progression rather than for a fixed period of time, any waning is likely to be captured in the modelling. The company added that there was less uncertainty in the survival extrapolations in its model because ARASENS was a more mature trial, and the general population mortality eventually merged. In addition, time spent in the hormone-relapsed metastatic prostate cancer setting was lower in the intervention arm, which could have been because of fewer treatment options being available at this stage. The committee acknowledged that the model and its extrapolations may already capture a gradual loss in treatment effect at an individual level. But it also agreed that scenarios exploring further impacts on treatment effect in the extrapolated part of the model would be useful to explore the extent to which the cost-effectiveness estimates depend on the assumption of constant treatment benefit. The committee concluded that the potential impact of treatment-effect waning was not known and added to the uncertainties.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.16 NICE's guide to the methods of health technology evaluation notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, decisions about the acceptability of a technology as an effective use of NHS resources will specifically consider the degree of uncertainty around the ICER, and aspects that relate to uncaptured benefits and non-health factors. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of the confidential commercial arrangements for darolutamide, its comparators, and other treatments after progression, the cost-effectiveness estimates cannot be reported here. The committee noted that the main differences in the company and EAG modelling was around modelling docetaxel disutility, and the latest data source for progression-free survival from ARCHES and STAMPEDE-2. It concluded that:

- adjusting docetaxel disutility for the proportion of people alive during 6 months (see section 3.14) had a negligible impact on the ICER, but the company's modelling approach was appropriate
- it preferred the latest progression-free survival estimates from ARCHES and STAMPEDE-2, but the reason for the large difference in treatment effectiveness between the interim and final assessments was uncertain.

The committee also noted the uncertainty in the cost-effectiveness results around:

- the impact of removing abiraterone from the network meta-analysis
- the potential impact of treatment-effect waning
- the clinical plausibility of modelled overall and progression-free survival estimates.

Acceptable ICER

3.17 The committee considered that a maximum acceptable ICER would be close to £20,000 per QALY gained, to take into account the impact of the uncertainties in the clinical plausibility of the modelled overall and progression-free survival, and the unknown impact of treatment-effect waning. Because of the confidential discounts, the cost-effectiveness results cannot be reported here. Applying confidential discounts for darolutamide plus ADT and docetaxel, its comparators and other treatments after progression, and considering its preferences, the committee noted that the cost-effectiveness estimates were within the maximum acceptable ICER range. That is, it considered darolutamide plus ADT and docetaxel to be an acceptable use of NHS resources. So, the committee recommended it for routine use in the NHS.

Other factors

Equality issues

3.18 The committee noted that people from Black, African and Caribbean family backgrounds are more likely to have an aggressive form of hormone-sensitive metastatic prostate cancer. But it concluded that its recommendation for darolutamide plus ADT and docetaxel would not have an effect on people protected by equality legislation different from the effect on the wider population.

Severity

3.19 The company did not consider that the severity weighting applied in this appraisal, and NICE's advice about conditions with a high degree of severity did not apply.

Innovation

3.20 The committee considered if darolutamide plus ADT and docetaxel was innovative. It did not identify any additional benefits not captured in the economic modelling. So, it concluded that all additional benefits of

darolutamide plus ADT and docetaxel had already been taken into account.

Conclusion

Recommendation

3.21 The committee agreed that its preferred cost-effectiveness estimates for darolutamide plus ADT and docetaxel were within the range considered an acceptable use of NHS resources. So, the committee concluded that it is recommended for treating hormone-sensitive metastatic prostate cancer.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance 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 draft guidance.

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

5 Evaluation committee members and NICE project team

Evaluation 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

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

Summaya Mohammad
Technical lead

Eleanor Donegan
Technical adviser

Jeremy Powell
Project manager

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