NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using capivasertib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: January 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using capivasertib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 04 February 2025
- Second evaluation committee meeting: 04 March 2025
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Capivasertib plus fulvestrant is not recommended, within its marketing authorisation, for treating hormone receptor (HR)-positive HER2-negative (defined as immunohistochemistry [IHC]0 or IHC1 positive, or IHC2 positive or in situ hybridisation [ISH]1 negative) locally advanced or metastatic breast cancer in adults that has:

- 1 or more PIK3CA, AKT1 or PTEN gene alterations
- recurred after or progressed on endocrine treatment.

1.2 This recommendation is not intended to affect treatment with capivasertib plus fulvestrant 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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for HR-positive HER2-negative locally advanced or metastatic breast cancer with 1 or more PIK3CA, AKT1 or PTEN gene alterations that has recurred (come back) after or progressed (got worse) on endocrine treatment is:

- alpelisib plus fulvestrant (for cancer with a PIK3CA alteration), or
- exemestane plus everolimus.

For this evaluation, the company asked for capivasertib to be considered only for people whose cancer has recurred or progressed after a CDK 4 and 6 inhibitor plus an aromatase inhibitor (a type of endocrine treatment). This does not include everyone who it is licensed for.

Clinical trial evidence shows that capivasertib plus fulvestrant increases how long people have before their cancer gets worse compared with fulvestrant.

Capivasertib plus fulvestrant has not been directly compared in a clinical trial with alpelisib plus fulvestrant or everolimus plus exemestane. The results of indirect comparisons are uncertain because:

- of differences in the populations in the clinical trials
- there are problems with the methods used to compare these treatments.

There are also uncertainties in the economic model, including the assumptions about how long the treatment effect lasts.

Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for capivasertib plus fulvestrant. So, capivasertib plus fulvestrant is not recommended.

2 Information about capivasertib plus fulvestrant

Marketing authorisation indication

2.1 Capivasertib (Truqap, AstraZeneca) is indicated 'in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative (defined as IHC 0 or 1+, or IHC 2+/ISH-) locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following recurrence or progression on or after an endocrine based regimen'.

Dosage in the marketing authorisation

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

Price

2.4 Capivasertib costs £5,850 per 64-pack of 200-mg tablets (excluding VAT; company submission). Fulvestrant costs £55.32 for 2 pre-filled syringes of 250 mg/5 ml solution for injection (excluding VAT; drugs and pharmaceutical electronic market information tool [eMIT], accessed

December 2024). The list price for 12 months of treatment is £77,088.12. The company has a commercial arrangement, which would have applied if capivasertib had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, 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.

HR-positive HER2-negative advanced breast cancer

3.1 Hormone receptor (HR)-positive HER2-negative advanced breast cancer is incurable and the aim of treatment is to delay progression and extend survival. If the cancer has alterations in the PIK3CA, AKT1 or PTEN genes, the focus of this evaluation, outcomes appear to be worse. Around 40% to 50% of people with HR-positive HER2-negative breast cancer have PI3K and AKT pathway alterations, of which over 75% are in the PIK3CA gene. The patient experts explained that being diagnosed with advanced breast cancer has a devastating impact on people's lives. People live with fear and anxiety, as well as the physical complications of the disease, and are aware that their survival is limited. This can also negatively affect their mental health. They explained that people with advanced breast cancer want a treatment that halts progression, extends life for as long as possible, has a good safety profile, and gives them a good quality of life. But, current options after initial endocrine treatment are limited (see section 3.2). The committee concluded that people with HR-positive HER2-negative advanced breast cancer have a high unmet clinical need.

Clinical management

Treatment options

3.2 The clinical experts explained that initial treatment for HR-positive HER2-negative advanced breast cancer is usually a cyclin-dependent kinase (CDK) 4 and 6 inhibitor plus an aromatase inhibitor (a type of endocrine treatment). After this initial treatment, the main options are alpelisib plus fulvestrant (if the cancer has a PIK3CA alteration) or everolimus plus exemestane (unless chemotherapy is needed because of symptomatic visceral disease; see NICE's technology appraisal guidance on alpelisib with fulvestrant for HR-positive HER2-negative PIK3CA-mutated advanced breast cancer [TA816] and on everolimus with exemestane for treating advanced breast cancer after endocrine therapy [TA421]). The clinical experts explained that there is an unmet need because current endocrine-based treatment is relatively ineffective after initial endocrine treatment plus a CDK 4 and 6 inhibitor. They said alpelisib plus fulvestrant is associated with toxicity that has substantially limited its use in the NHS. And that everolimus plus exemestane has low response rates and exemestane is less effective for ESR1-positive cancer, which is up to 50% of cancers in this population. They said that treatments that make endocrine-based treatment more effective after progression on endocrine treatment plus a CDK 4 and 6 inhibitor are important. The clinical experts explained that if endocrine-based treatment fails, chemotherapy is the main option, but delaying this is highly important for patients because of the toxicity it involves. They added that they believed capivasertib plus fulvestrant is a highly effective and well-tolerated targeted treatment that represents a step change in managing breast cancer with PIK3CA, AKT1 or PTEN alterations. The clinical experts said that the toxicity is much lower with capivasertib plus fulvestrant than alpelisib plus fulvestrant, so quality of life is likely to be better on treatment. The committee noted that side effects including hyperglycaemia, rash and stomatitis (an inflamed and sore mouth) were listed in the summary of product characteristics for

capivasertib. The clinical experts explained that these side effects are more significant with alpelisib plus fulvestrant or everolimus plus exemestane. They said that there are substantial challenges with managing hyperglycaemia associated with alpelisib plus fulvestrant. For example, treatment requires learning to use a glucose monitor because of the risk of diabetes. The clinical experts added that rash was a more serious problem with alpelisib and that stomatitis could be a serious problem with everolimus. The patient experts also highlighted the value of having a well-tolerated treatment that delays progression and targets the AKT1 or PTEN gene mutation, noting that there are currently none available. The committee recognised the limitations with existing treatments, the advantages of capivasertib plus fulvestrant, and the importance of having a targeted treatment for HR-positive HER2-negative advanced breast cancer with PIK3CA, AKT1 or PTEN alterations.

Population

3.3 The marketing authorisation for capivasertib plus fulvestrant is for people whose cancer has recurred or progressed on or after an endocrine-based regimen. The company submitted evidence for a narrower population: people whose cancer has recurred or progressed after a CDK 4 and 6 inhibitor plus an aromatase inhibitor. The company said that this positioning reflected the anticipated use of capivasertib plus fulvestrant in the current UK treatment pathway. It did not anticipate capivasertib being used for people who had not already had a CDK 4 and 6 inhibitor. The committee noted the clinical experts' comments that a CDK 4 and 6 inhibitor plus an aromatase inhibitor is standard initial treatment for HR-positive HER2-negative advanced breast cancer (see section 3.2). It also noted that the company's positioning of capivasertib plus fulvestrant reflected that of alpelisib plus fulvestrant in TA816. The committee concluded that the company's positioning of capivasertib plus fulvestrant after progression on a CDK 4 and 6 inhibitor plus an aromatase inhibitor was appropriate and in line with expected clinical use.

Comparators

3.4 The company submitted evidence against 2 comparators: alpelisib plus fulvestrant for PIK3CA-altered breast cancer and everolimus plus exemestane. It said that these were the standard treatments after initial endocrine treatment with a CDK 4 and 6 inhibitor plus an aromatase inhibitor, where capivasertib would be used. It said it expected capivasertib plus fulvestrant to be used mainly in place of alpelisib plus fulvestrant because most people with PIK3CA and AKT pathway-altered tumours have PIK3CA alterations. The clinical experts agreed that these are the standard treatments after initial endocrine treatment (see section 3.2). The committee concluded that alpelisib plus fulvestrant for PIK3CA-altered breast cancer and everolimus plus exemestane were the relevant comparators for the evaluation.

Clinical effectiveness

CAPItello-291 trial

3.5 The key clinical trial, CAPItello-291, was a randomised, double-blind, placebo-controlled phase 3 trial comparing capivasertib plus fulvestrant with placebo plus fulvestrant. It included people whose HR-positive HER2-negative breast cancer had recurred or progressed on or after treatment with an aromatase inhibitor with or without a CDK 4 and 6 inhibitor. People who had previous fulvestrant were excluded. A subgroup of people in the trial had PI3K and AKT pathway-altered (PIK3CA, AKT1 or PTEN) tumours. Results showed that capivasertib plus fulvestrant significantly improved progression-free survival (median 7.3 months; 95% confidence interval [CI] 5.5 to 9.0) compared with placebo plus fulvestrant (median 3.1 months; 95% CI 2.0 to 3.7) in people with PI3K and AKT pathway-altered tumours. Results were similar for people who had previously had a CDK 4 and 6 inhibitor (the company considers this data confidential, so it is not reported here). For overall survival, there was not enough data for a formal analysis. In people with PI3K and AKT pathway-

altered tumours, overall survival was better on capivasertib plus fulvestrant, although this was not statistically significant (hazard ratio 0.69; 95% CI 0.45 to 1.05). The committee concluded that capivasertib plus fulvestrant improved progression-free survival compared with placebo plus fulvestrant.

Indirect treatment comparisons

3.6 Because there was no direct evidence comparing capivasertib plus fulvestrant with alpelisib plus fulvestrant or everolimus plus exemestane, the company did indirect treatment comparisons. The network meta-analysis (NMA) included 10 randomised controlled trials. Data for capivasertib plus fulvestrant came from the CAPItello-291 and FAKTION trials; for alpelisib plus fulvestrant from the SOLAR-1 trial, and for everolimus plus exemestane from the BOLERO-2 and BOLERO-5 trials.

Heterogeneity in baseline characteristics

3.7 The NMA used data from the subgroups of people in CAPItello-291 and FAKTION who had PI3K and AKT pathway-altered tumours, and the PIK3CA-altered subgroup from SOLAR-1.The other trials did not report who had PI3K and AKT pathway-altered tumours. The EAG said that there was evidence that PIK3CA, AKT1 and PTEN alterations are treatment effect modifiers for capivasertib plus fulvestrant, and PIK3CA alteration a modifier for alpelisib plus fulvestrant. It added that ideally the indirect treatment comparisons would use subgroups with PI3K and AKT pathway alteration from all studies. The company accepted that there was some uncertainty in the results because of this but said that it had fully explored the available data. It noted that there was no evidence that PI3K and AKT pathway alteration was a treatment effect modifier for the other treatments in the network. Also, that it was unknown how much variation in PI3K and AKT pathway alteration could bias the results. The EAG was also concerned about heterogeneity in other baseline characteristics, including differences in HER2 status, previous treatment, and Eastern

Cooperative Oncology Group (ECOG) performance status. The EAG said that the impact of the differences was difficult to predict but it made the results uncertain. A clinical expert noted that SOLAR-1 (alpelisib plus fulvestrant) and BOLERO-2 (everolimus plus exemestane) were before CDK 4 and 6 inhibitors were adopted. So response rates and progression-free survival between these studies and CAPItello-291 (capivasertib plus fulvestrant) cannot be directly compared. They also noted that endocrine monotherapy is less effective after progression on a CDK 4 and 6 inhibitor plus an aromatase inhibitor, as shown in the fulvestrant control arms in:

- CAPItello-291 (69% previously had a CDK 4 and 6 inhibitor), in which median progression-free survival was 3.1 months; and
- SOLAR-1 (6% previously had a CDK 4 and 6 inhibitor), in which median progression-free survival was 5.7 months.

A committee member noted that, because of this, the efficacy of the comparators may be underestimated if fulvestrant was being used as the anchor in the NMA. The clinical expert said that although the absolute benefit is lower with fulvestrant after a CKD 4 and 6 inhibitor, there was no biological reason for there to be a difference in the relative benefit. But the committee noted that previous CDK4 and 6 inhibitor treatment appeared to have a substantial impact on overall survival in the fulvestrant arm of CAPItello-291 while the capivasertib arm appeared to be unaffected by previous CDK4 and 6 inhibitor use. The company considers the results from the CDK4 and 6 inhibitor subgroup confidential so they are not reported. The committee considered that there was considerable heterogeneity in the baseline characteristics of the studies included in the NMA, particularly for PI3K and AKT pathway status and previous CDK 4 and 6 inhibitor use. It thought that the differences in the populations may have compromised the validity of the results but that the magnitude of any bias was difficult to predict. The committee concluded that the results of the NMA were highly uncertain.

Economic model

3.8 The company submitted a partitioned survival model to estimate the cost effectiveness of capivasertib plus fulvestrant compared with alpelisib plus fulvestrant and with everolimus plus exemestane. It had 3 health states: progression-free, progressed and dead. The model had a lifetime time horizon (20 years). The committee considered that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making.

Modelling of long-term progression-free survival

3.9 To estimate long-term progression-free survival, the company fitted parametric survival models (exponential, log-normal, Weibull, log-logistic, gamma, generalised gamma and Gompertz) to the patient-level data of the placebo plus fulvestrant arm from CAPItello-291 (the common comparator in the NMA). It chose the log-normal distribution in its base case (preferred by 1 out of 5 of the company's clinical experts), based on goodness of fit, visual inspection and clinical opinion. The company explored the log-logistic distribution in a scenario, noting that generalised gamma was also suitable (these 2 were preferred by 3 out of 5 of the company's clinical experts). The EAG preferred the log-logistic distribution for its base case because it had the best fit on the Akaike information criterion (AIC) and Bayesian information criterion (BIC) and it was preferred by most of the company experts. The committee concluded that the log-logistic model was the most appropriate to estimate long-term progression-free survival because it had the best fit to the trial data and was preferred by most of the company's clinical experts.

Modelling of long-term relative treatment effect

3.10 The company estimated progression-free survival and overall survival for all 3 treatments using the hazard ratios from the NMA. It applied these to the modelled placebo plus fulvestrant progression-free survival curve for people with PI3K and AKT pathway-altered tumours who had previous

CDK 4 and 6 inhibitor and endocrine treatment. This was on the assumption that proportional hazards applied for the studies in the network (that is, the assumption that the relative hazards remain constant over time for each treatment comparison). The company analysed the studies for evidence of non-proportional hazards and found that it varied from none to strong:

- for progression-free survival:
  - none, 1 study
  - weak, 4 studies
  - moderate, 2 studies
  - strong, 3 studies
- for overall survival (4 studies did not report this outcome):
  - weak, 4 studies
  - moderate, 2 studies.

The company said there was no consistent evidence that the proportional hazards assumption does not hold. It said the fixed effects model had the best statistical fit to the trial data, so it used the hazard ratios from this in its base-case model. After an EAG request to explore time-varying approaches, the company presented a piecewise NMA using 2 different hazard ratios and time periods based on visual inspection of the Kaplan–Meier data. The company said that it chose this approach to allow incorporation into the existing model and because more complex methods would have been challenging with the data available. For progression-free survival it chose time periods of 0 to 3 months and over 3 months (and 0 to 2 months and over 2 months in another scenario). For overall survival it chose 0 to 6 months and over 6 months. The EAG said that a time-varying analysis was more appropriate because of evidence that the proportional hazards assumption did not hold for progression-free survival in some trials (and possibly for overall survival). The EAG thought that the company's piecewise NMA was an improvement over the constant hazard

ratio NMA and used this in its base case. But it noted that the reasons for the time periods chosen were not well justified. It also preferred an NMA using a time-varying parametric model. The committee agreed with the EAG and thought that the piecewise time-varying NMA did not properly explore a time-varying hazard ratio. It thought that the rationale for the timepoints was not properly justified and that basing them on the Kaplan–Meier data was not appropriate because this data provides a survival function, not a hazard function. The committee also noted that there was a large change in hazard ratios between the 2 timepoints. The committee concluded that neither the constant nor piecewise NMAs were appropriate for modelling relative treatment effect. It concluded that it would prefer to see fully time-varying analyses for modelling survival, such as using a fractional polynomial model.

Treatment waning

3.11 The company did not incorporate treatment waning into its model. That is, the model assumed the relative benefits of treatment continued at the same level over time. The company said it believed that the time-varying NMA accounted for treatment waning because of the 3-month (progression-free survival) and 6-month (overall survival) cutoff points, with the hazard ratio increasing at the second time point. The EAG disagreed that the company's time-varying scenario would account for waning in the longer-term period. The EAG noted that there was some indication of treatment effect waning for alpelisib plus fulvestrant and for everolimus plus exemestane, and felt treatment effect waning should be explored. In its base case, the EAG set the hazard ratios for progression-free survival and overall survival to 1 after 24 months for all treatments compared with fulvestrant, and after 36 months in a scenario. It accepted that the time points were arbitrary but considered that they were plausible and useful to explore. The company said the analyses were not reasonable, evidence based, or aligned with TA816, which applied treatment waning at 5 years. The committee noted that setting the hazard

ratio to 1 after 24 months had a large impact on the incremental cost-effectiveness ratio (ICER). It agreed with the EAG that the company's time-varying piecewise scenario did not account for treatment waning. It noted the lack of data to inform the period beyond 5 years and so it was not convinced by the company's 6-month cut off for overall survival. It thought that an indefinite duration of treatment effect was unlikely and that the higher hazard ratios at the second time point indicated treatment waning. It also noted that only a small number of people were still on treatment at 2 years, so it was not implausible to set waning at 2 years. It also noted that a hazard ratio of 1 did not imply all treatment benefit disappearing, but that the risk of death was similar for all groups after 2 years. A clinical expert said that it was reasonable to assume the same treatment waning characteristics would apply for capivasertib plus fulvestrant and its comparators. The committee concluded that, unless a time-varying analysis (see section 3.10) showed strong evidence of no treatment waning, it would like to see analyses incorporating treatment waning, including waning at 2 years and 3 years.

Health-related quality of life

3.12 The company measured quality of life in the overall population of CAPItello-291 using the EQ-5D-5L. It mapped this to the EQ-5D-3L to derive utilities, in line with the NICE reference case. The committee considered how valid the utility values were. It noted the EAG's comments that the difference between the utility values before and after progression was small compared with previous NICE appraisals in this population. The company considers these values confidential and so they cannot be reported. The EAG suggested that utility data may not have been collected for long enough after progression. The company pointed out that its utility values had been estimated using trial data, in line with the NICE reference case. It noted that in TA421 vignettes were used to estimate utility, which was not in line with the NICE reference case. The company said that health-related quality of life may not have declined substantially

after capivasertib plus fulvestrant was stopped because people went on to have other treatments. The committee asked how progression was determined. A clinical expert said that progression was usually determined by CT scans every 3 months. The clinical expert added that people also developed other symptoms that could significantly worsen quality of life and be a psychological burden. Both clinical experts agreed that toxicity was much lower with capivasertib plus fulvestrant compared with alpelisib plus fulvestrant and so likely to lead to better quality of life on treatment (see section 3.2). The committee recognised capivasertib's improved tolerability but felt that the post-progression utility value was very high. It noted that in TA816 a post-progression utility value of 0.69 had been used from Mitre et al. (2016). It appreciated that the value from Mitre et al. was considered uncertain and possibly overestimated. The committee also noted that in the current evaluation the company had presented scenario analyses using values of 0.70, 0.65 and 0.60, and that the EAG had used the value of 0.60 in an exploratory analysis. The committee accepted that the appropriate utility value for the modelled health state after disease progression is uncertain. It concluded that in the new analyses from the company (see section 3.19) it would like to see the company and EAG scenarios, plus a scenario using the 0.69 value from Mitre et al. to explore this uncertainty.

Costs

Genetic testing

3.13 Treatment with capivasertib plus fulvestrant requires genomic testing for PIK3CA, AKT1 or PTEN alterations. The company did not include the cost of testing for these alterations in its base case. This is because testing for PIK3CA alterations (the most common PI3K and AKT pathway alteration) is done routinely in UK clinical practice since NICE recommended alpelisib plus fulvestrant in 2022 (see NICE's technology appraisal guidance on alpelisib with fulvestrant). The company did a scenario

analysis that showed that including additional testing costs for AKT1 and PTEN alterations had little impact on the estimated ICER. The Cancer Drugs Fund lead said that although PIK3CA alterations are tested for, AKT1 and PTEN are not, so additional costs to test for them needed incorporating into the model. The committee concluded that the costs of testing for AKT1 and PTEN alterations should be included in the model.

Time to treatment discontinuation

3.14 In the company's model, people on all treatments were assumed to continue until disease progression, unacceptable toxicity or until they withdrew consent. To model time to treatment discontinuation for capivasertib plus fulvestrant, the company calculated the ratio between time to treatment discontinuation and progression-free survival in CAPItello-291. It applied this ratio to the modelled progression-free survival curve for all treatments. The company considers the figure for the ratio confidential so it is not reported here. This was a pragmatic approach for alpelisib plus fulvestrant and everolimus plus exemestane because there was no publicly available data on time to treatment discontinuation. The EAG noted that discontinuation rates because of disease progression and adverse events differed substantially in the relevant trials:

- capivasertib plus fulvestrant (CAPItello-291); 58.9% disease progression, 13% adverse events
- alpelisib plus fulvestrant (SOLAR-1); 37% disease progression, 25% adverse events
- everolimus plus exemestane (BOLERO-2); 55% disease progression, 19% adverse events.

The EAG said this suggests that the relative proportion of people stopping treatment because of reasons other than progression differs by treatment. The EAG used the company's value for time to treatment discontinuation in its base case. But it modelled the impact of a shorter time to discontinuation for the comparators (on the basis that adverse events

were worse with the comparators) in a scenario to test its impact. The clinical experts said that if people have side effects, usually treatment will continue at the same dose, as long as they are tolerable. If side effects are severe, treatment might stop temporarily and be restarted at a lower dose and only a small number will stop treatment completely. In the absence of evidence and, based on what it had heard from the clinical experts about the toxicity profiles of the treatments, the committee accepted the company's base-case assumption.

Relative dose intensity

3.15 The company modelled mean relative dose intensity (RDI) for capivasertib plus fulvestrant and everolimus plus exemestane. RDI is a measure of how much of the planned dose of drug a participant actually has in a trial. Someone may not have the full planned dose, for example, because of toxicity, which may mean the dose needs to be reduced or delayed. For alpelisib plus fulvestrant, only the median RDI was available from SOLAR-1 (82.7%), so the company assumed a 100% RDI in its base case, with a scenario analysis applying the median RDI. It said this was because means and medians were not the same; the data could be skewed, so means were preferred. The EAG pointed out that if the median RDI for alpelisib plus fulvestrant was 82.7%, this showed that there were delayed or reduced doses. It said that assuming 100% RDI would overestimate its cost. The committee agreed with the EAG's comments. The company provided a scenario that assumed the same RDI for alpelisib plus fulvestrant as for capivasertib plus fulvestrant, which the EAG used in its base case. The company considers that this value is confidential and so it is not reported. The clinical experts said that a 100% RDI was not plausible and reiterated that alpelisib was the least well tolerated of the treatments (see section 3.2). A clinical expert said that alpelisib was likely to have the lowest RDI of all the treatments. The committee concluded that using a 100% RDI would overestimate costs for alpelisib plus fulvestrant. It also concluded that it would prefer the median RDI of 82.7%

to be used in the model, in the absence of any other evidence. But it also said that it would like to see more evidence on the appropriate RDI for alpelisib plus fulvestrant.

Severity

3.16 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's manual on health technology evaluations. The proportional QALY shortfall showed that the condition met the threshold for applying a QALY weight of 1.2, which the EAG agreed with. The committee noted the uncertainty with the results of the indirect treatment comparisons (see section 3.7), the modelling of long-term survival (see sections 3.9 and 3.10), and the health state utility values used in the model (see section 3.12). The committee concluded that it would like to see the results of new analyses (see section 3.19) and their effect on the QALY weight before it made a decision on severity.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.17 Because of confidential commercial arrangements for capivasertib, alpelisib, fulvestrant, and one of the post-progression treatments, the cost-effectiveness results are confidential and cannot be reported here. The committee considered that the cost-effectiveness estimates comparing capivasertib plus fulvestrant with alpelisib plus fulvestrant and with everolimus plus exemestane were highly uncertain. It concluded that further analyses were needed to determine the most plausible estimates for decision making.

Acceptable ICER

3.18 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee appreciated the high unmet need of people with HR-positive HER2-negative advanced breast cancer. It also recognised that capivasertib is an innovative treatment that the clinical experts considered to be a step change in managing breast cancer with PIK3CA, AKT1 or PTEN alterations. But it was concerned about the high level of uncertainty, specifically:

- whether the differences between the populations in terms of PI3K and AKT pathway status and previous treatment with CDK 4 and 6 inhibitors biased the indirect treatment comparisons (see sections 3.6 and 3.7)
- the modelling of long-term overall and progression-free survival and whether it was more appropriate to use a fully time-varying analysis and incorporate treatment waning (see sections 3.9 to 3.11)
- the most appropriate utility value to use for the post-progression health state (see section 3.12).

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

Summary of additional analyses

3.19 The committee requested the following additional analyses:

- using a log-logistic model to estimate long-term progression-free survival (see section 3.9)

- exploring time-varying hazard ratios using fully time-varying analyses to model survival, such as a fractional polynomial model (see section 3.10)
- incorporating treatment waning in the model, including waning at 2 years and 3 years (see section 3.11)
- scenarios using exploratory health state utility values of 0.60, 0.65 and 0.70, and the value of 0.69 from TA816 (Mitre et al. 2016) for the post-progression health state (see section 3.12)
- incorporating the costs of testing for AKT1 and PTEN alterations (see section 3.13)
- incorporating an RDI of 82.7% for alpelisib plus fulvestrant and evidence-based scenarios for alternative RDIs (see section 3.15).

Other factors

Equality

3.20 The committee did not identify any equality issues.

Uncaptured benefits

3.21 The committee considered whether there were any uncaptured benefits of capivasertib. It did not identify additional benefits of capivasertib not captured in the economic modelling. So the committee concluded that all additional benefits of capivasertib had already been taken into account.

Conclusion

Recommendation

3.22 The committee recognised that capivasertib plus fulvestrant is an effective treatment after a CDK 4 and 6 inhibitor plus an aromatase inhibitor. But the company's and EAG's cost-effectiveness estimates were very uncertain. The committee concluded that it needed further analyses to agree the most appropriate decision making ICERs. So capivasertib plus fulvestrant is not recommended for HR-positive, HER2-negative advanced

breast cancer with PIK3CA, AKT1 or PTEN alterations after endocrine-based treatment.

4 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 A.

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

Radha Todd

Chair, technology appraisal committee A

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, a project manager and an associate director.

Emilene Coventry

Technical lead

Zoe Charles

Technical adviser

Jennifer Upton

Project manager

Janet Robertson

Associate director

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