National Institute for Health and Care Excellence

Health Technology Evaluation

Capivasertib with fulvestrant for treating hormone receptor-positive HER2-negative advanced breast cancer after endocrine treatment [ID6370]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	It is appropriate to evaluate this topic via the Single Technology Appraisal route, as capivasertib in combination with fulvestrant is addressing an unmet need for additional endocrine-based targeted therapy options to delay chemotherapy initiation for patients with hormone receptor-positive (HR+)/HER2- advanced breast cancer. There are no treatment options available that target all three genetic alterations, AKT1, PTEN and PIK3CA, of the PI3K/AKT pathway. These genetic alterations exert a pivotal role in cell growth, proliferation, survival, and metabolism,1 and are frequently dysregulated in various cancers including breast cancer.1, 2 AKT is the key node in the PI3K/AKT pathway.1,3 Capivasertib is a novel, first-in-class highly selective pan-AKT (AKT1, AKT2 and AKT3) inhibitor.3 If approved, capivasertib will be the first available AKT inhibitor for the treatment of locally advanced or metastatic HR+/HER2− breast cancer that has progressed following recurrence or progression on endocrine therapy.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
		In addition, hyperactivation of the PI3K/AKT pathway can exist as a mechanism of resistance to endocrine therapy regardless of presence or absence of PI3K/AKT/PTEN alterations.2,4 This highlights the benefits of capivasertib in combination with fulvestrant in all patients with HR+/HER2- advanced breast cancer.	
	METUPUK	This is an important evaluation for patients who have progressed on endocrine treatment. There is currently no AKT inhibitor available on the NHS in England for metastatic breast cancer with PIK3CA, AKT1 or PTEN alterations. This evaluation addresses an unmet need.	Thank you for your comment. No action required.
	Breast Cancer Now	This is an appropriate topic for evaluation as a single technology appraisal	Thank you for your comment. No action required.
Wording	AstraZeneca	Yes	Thank you for your comment. No action required.
	METUPUK	Yes although if the marketing authorisation is restricted to patients with alterations in the PIK3CA, AKT1 or PTEN genes, then this should be reflected in the wording of the remit.	Thank you for your comment. Capivasertib with fulvestrant does not currently have a UK marketing authorisation for hormone receptor-positive HER2-negative advanced breast cancer. So the remit of the scope has been

Section	Stakeholder	Comments [sic]	Action
			kept broad. No action required.
	Breast Cancer Now	We would note that this treatment has not yet received a marketing authorisation in the UK, so we are unable to judge whether the evaluation remit will sit in line with its marketing authorisation.	Thank you for your comment. No action required.
Timing issues	AstraZeneca	The urgency for this appraisal arises from the paucity of treatment options reimbursed by the NHS for patients with HR+/HER2- locally advanced or metastatic breast cancer, in particular for those patients who have AKT1, PTEN and/or PIK3CA alterations driving tumour formation. Currently there are no treatment options for patients who have other PI3K/AKT pathway dysregulations that are not PIK3CA hotspot mutations, capivasertib presents an option for these patients as it also targets AKT1 and PTEN alterations in addition to targeting PIK3CA alterations. AstraZeneca proposes a timely appraisal should take place given the current unmet need for targeted treatment options for patients with PI3K/AKT pathway dysregulation.	Thank you for your comment. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-ta11513
	METUPUK	There is an unmet need for additional lines of therapy for patients with hormone receptor-positive HER2-negative MBC. Capivasertib is the first AKT inhibitor which has been appraised for use in metastatic breast cancer. It is the only drug available in its class at the moment, and is an innovative treatment. Patients value targeted treatments over untargeted cytotoxic chemotherapy. Therefore we consider this evaluation to be urgent.	Thank you for your comment. Thank you for your comment. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/

Section	Stakeholder	Comments [sic]	Action
			guidance/indevelopment/gid-ta11513
	Breast Cancer Now	Additional treatment options are needed for patients with ER-positive, HER2-negative locally advanced or metastatic cancer which has progressed following endocrine treatment. This is a first in class AKT inhibitor so we hope this appraisal can progress in a timely manner and open up additional treatment options.	Thank you for your comment. Thank you for your comment. NICE will evaluate the technology within its marketing authorisation and has scheduled this topic into its work programme. For more information, please see https://www.nice.org.uk/guidance/indevelopment/gid-ta11513
Additional comments on the draft remit	AstraZeneca	None	No action required.
	METUPUK	No additional comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	As PIK3CA/AKT1/PTEN-altered patients have been identified as a relevant subgroup, we propose to include epidemiological data on the frequency of these mutations as part of the background information. PI3K/AKT pathway mutations have been found in 40.8% of patients with HR+/HER2- locally advanced or metastatic breast cancer.[3]	Thank you for your comment. The scope background provides a brief overview of the condition and treatment

Section	Consultee/ Commentator	Comments [sic]	Action
		The NICE CG81 was first published in 2009 and last updated in 2017.[5] Therefore, the latest CG81 predates the NICE recommendations of CDK4/6 inhibitors (CDK4/6i) and aromatase inhibitor (AI) regimens as treatment options for HR+/HER2-, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults (TA563, TA496 and TA495),[6-8] which have since become the standard of care. Therefore, when using CG81 for making treatment decision choices, it should be taken into consideration that recommendations from newer NICE guidance (TA563, TA496, TA495, TA816, TA725, TA687, TA836)[6-12] have not been explicitly included, and the treatment pathway has evolved towards using more combination treatments[15,20]. UK clinician feedback has confirmed that CDK4/6i + AI is the current first-line standard of care (SoC) for locally advanced or metastatic HR+/HER2- breast cancer.	pathway. The background section has been updated to include 'PI3K/AKT pathway mutations are found in approximately 40% of people with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer', 'Fulvestrant is not recommended for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer (NICE technology appraisal 503)' and 'Fulvestrant is not recommended for use following anti-oestrogen therapy, as an alternative to aromatase inhibitors (NICE technology appraisal 239), however, it is sometimes used after exemestane and tamoxifen in people

Section	Consultee/ Commentator	Comments [sic]	Action
			who would otherwise receive chemotherapy.
	METUPUK	If the marketing authorisation is restricted to tumours with alterations in PIK3CA, AKT1 or PTEN then a brief explanation of what these mutations are and how they are tested could be included for completeness.	Thank you for your comment. The scope background provides a brief overview of the condition and treatment pathway. It has been updated to include 'PI3K/AKT pathway mutations are found in approximately 40% of people with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer'. 'Fulvestrant is not recommended for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer (NICE technology appraisal 503)' and 'Fulvestrant is not recommended for use following anti-oestrogen therapy, as an

Section	Consultee/ Commentator	Comments [sic]	Action
			alternative to aromatase inhibitors (NICE technology appraisal 239), however, it is sometimes used after exemestane and tamoxifen in people who would otherwise receive chemotherapy. No other action required.
	Breast Cancer Now	We consider this information to be accurate and complete	Thank you for your comment. No action required.
Population	AstraZeneca	The target population for this appraisal is [redacted]	Thank you for your comment. Capivasertib with fulvestrant does not currently have a UK marketing authorisation for hormone receptor-positive HER2-negative advanced breast cancer. So the population in the scope has been kept broad. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	METUPUK	Yes	Thank you for your comment. No action required.
	Breast Cancer Now	Yes to the best of our knowledge. This population may need to be refined further on the basis of a UK marketing authorisation.	Thank you for your comment. Capivasertib with fulvestrant does not currently have a UK marketing authorisation for hormone receptor-positive HER2-negative advanced breast cancer. So the population in the scope has been kept broad. No action required.
Subgroups	AstraZeneca	AstraZeneca agree that the PIK3CA/AKT1/PTEN-altered subgroup is an appropriate subgroup to consider, if the evidence allows	Thank you for your comment. No action required.
	METUPUK	Yes, the subgroups listed are appropriate	Thank you for your comment. No action required.
	Breast Cancer Now	The subgroups suggested within the scope are appropriate. In the CAPItello-291 clinical trial the PIK3CA/AKT1/PTEN-altered subgroup of patients showed a greater difference in median progression free survival, compared to placebo, than the overall population compared to placebo. As a result it is appropriate to consider them as a subgroup.	Thank you for your comment. No action required.

Comparators	AstraZeneca	**Endocrine monotherapy (including fulvestrant, tamoxifen, exemestane) +/- chemotherapy** Endocrine monotherapy +/- chemotherapy is not a relevant comparator for this appraisal. Endocrine monotherapies include selective oestrogen receptor modulators (tamoxifen), selective oestrogen receptor degraders (fulvestrant) and AIs (anastrozole, letrozole, exemestane). Since the emergence of CDK4/6i + AI regimens (TA563, TA496 and TA495)[6-8], and the confirmation by UK clinical experts that these form first-line SoC in UK, endocrine monotherapy is now reserved for a small number of cases where patients cannot tolerate a CDK4/6i regimen due to comorbidities and/or poor performance status (e.g. elderly). These patients are unlikely to be suitable for a combination treatment such as capivasertib in combination with fulvestrant according to UK clinician feedback. In addition, for patients with confirmed PI3K/AKT pathway alterations, a treatment option targeting their specific tumour driver mutation would be more beneficial than endocrine monotherapy targeting solely oestrogen receptor signalling. Therefore, endocrine therapy (including tamoxifen and fulvestrant monotherapy) +/- chemotherapy is not a relevant comparator for this appraisal. **Fulvestrant monotherapy** Fulvestrant is not recommended by NICE, within its marketing authorisation, for treating locally advanced or metastatic oestrogen-receptor positive breast cancer in postmenopausal women who have not had endocrine therapy before (TA503), or for postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy (TA239).[21,22] Therefore, it is not routinely commissioned in England. This has been highlighted in other relevant appraisals in this patient population.[9,14] If patients are suitable for combination therapy such as everolimus with exemestane, or alpelisib with fulvestrant, such regimens would be preferred over fulvestrant monotherapy, so the patient can benefit from the improved efficacy associated with combination antihormonal regimens. As capivasertib with fulvestrant will only be used in patients who are suitable for combination	Thank you for your comments. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal. In line with NICE Clinical Guidelines 81 (CG81), we acknowledge that chemotherapy is offered if the disease is rapidly progressing, or if the patient is in visceral crisis. The final scope has been updated by removing 'Endocrine therapy with or without chemotherapy' and 'Chemotherapy' from the list of comparators. Clinical advice to NICE suggests that fulvestrant could be used in NHS clinical practice. In line with CAPItello-291 trial, it is expected that capivasertib with fulvestrant is expected

		therapy, fulvestrant monotherapy in second-line is not a relevant treatment option. It is therefore not a relevant comparator for this appraisal. **Exemestane monotherapy** Exemestane monotherapy is not a relevant comparator for this appraisal. ESMO notes that ET alone in the first-line setting should be reserved for the small group of patients with comorbidities or a PS that precludes the use of CDK4/6i combinations. Therefore, the number of patients who may receive exemestane in second-line would be even smaller. Capivasertib in combination with fulvestrant is not a likely option in the small number of patients in whom exemestane would be used in second-line. UK clinicians stated that exemestane monotherapy is not a frequently used regimen, as non-steroidal AIs are typically preferred, and use of exemestane on its own will lead to ineligibility for the everolimus and exemestane combination. It is therefore not a relevant comparator. This is in alignment with other technology appraisals in this setting.[14] **Chemotherapy** Chemotherapy is not a relevant comparator for this appraisal. Chemotherapy is offered if the disease is rapidly progressing, or the patient is in visceral crisis as per CG81.[5] ESMO guidelines state chemotherapy after at least 2 lines of endocrine-based therapy (excluding patients with visceral crisis).[15] Additionally, ESMO Guidelines also recommend that patients with endocrine resistant tumours should be considered for chemotherapy. If a patient which progresses on a CDK4/6i + ET is in imminent organ failure or short PFS on endocrine-based therapy is anticipated, the only option recommended by ESMO and also reimbursed in the UK is chemotherapy. [15] This indicates patients suitable for chemotherapy are viewed as endocrine treatment-resistant, and are unlikely to benefit from further endocrine treatment. Furthermore, clinician feedback has indicated that, in the attempt to delay chemotherapy initiation for as long as possible, chemotherapy is offered when all suitable endocrine options have been exhausted and/or the patient	to be used in fulvestrant naïve patients. Therefore, the final scope has also been updated by adding 'Fulvestrant' to the list of comparators.

		is deemed endocrine-insensitive. Multiple recent NICE technology assessments report clinician and patient preference towards delaying chemotherapy (eg TA496, TA725, TA687).[7,10,11] As patients need to be endocrine treatment-sensitive to benefit from capivasertib and fulvestrant, chemotherapy regimens are not relevant comparators. **CDK4/6i in combination with fulvestrant** CDK4/6i (abemaciclib, ribociclib, palbociclib) in combination with fulvestrant is not a relevant comparator for this appraisal. There is consensus that CDK4/6i + AI regimens (TA563, TA496 and TA495)[6-8] form first-line SoC in UK clinical practice and this particular combination is received by the majority of patients who are eligible for treatment with CDK4/6i + ET. CDK4/6i + fulvestrant is typically received by patients for whom CDK4/6i + AI was not clinically appropriate or exceptional circumstances where CDK4/6i could not be given in first-line, but this is in the minority of patients. CDK4/6i re-challenge is currently not reimbursed in the UK, and patients would be ineligible for CDK4/6i + fulvestrant following SoC CDK4/6i + AI in first-line.[10-12] Additionally, CDK4/6i + fulvestrant as first line therapy would render patients ineligible for some second line combination therapies such as alpelisib + fulvestrant which requires patients to be fulvestrant naïve for treatment eligibility. In summary, AstraZeneca propose that CDK4/6i with fulvestrant, exemestane, tamoxifen, endocrine therapy +/- chemotherapy, and chemotherapy are not relevant comparators for this appraisal and should be removed from the scope. This is in alignment with other technology appraisals in this setting.[9,14] **The relevant comparators for the scope of this assessment are:** • **everolimus with exemestane, and** **alpelisib with fulvestrant.**	

Section	Consultee/ Commentator	Comments [sic]	Action
	METUPUK	No comments because we are a patient advocacy charity. We would prefer clinical input here.	Thank you for your comment. No action required.
	Breast Cancer Now	Where the term 'endocrine therapies with or without chemotherapy' is used does 'chemotherapy' refer to cytotoxic chemotherapy (which is not commonly given in combination with endocrine therapy - so would not be a suitable comparator) or endocrine therapy and drugs such as CDK 4/6 or alpelisib or everolimus? Please clarify in order for us to respond appropriately. It would be helpful to specifically list which endocrine therapies are being considered as comparators. We would also question which chemotherapy drug/drugs are being considered, as some patients may be given single agent capecitabine chemotherapy rather than everolimus plus exemestane.	Thank you for your comments. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal. Chemotherapy in the scope refers to cytotoxic chemotherapy. In line with CG81, we acknowledge that chemotherapy is offered if the disease is rapidly progressing, or if the patient is in visceral crisis. The final scope has been updated by removing 'Endocrine therapy with or without chemotherapy' and 'Chemotherapy' from

Section	Consultee/ Commentator	Comments [sic]	Action
			the list of comparators. Clinical advice to NICE suggests that fulvestrant could be used in NHS clinical practice. In line with CAPItello-291 trial, it is expected that capivasertib with fulvestrant is expected to be used in fulvestrant naïve patients. Therefore, the final scope has also been updated by adding 'Fulvestrant' to the list of comparators.
Outcomes	AstraZeneca	AstraZeneca considers the outcome measures listed in the draft scope are appropriate and comprise the important outcomes for the assessment of efficacy, health-related benefits and harms associated with capivasertib and fulvestrant.	Thank you for your comment. No action required.
	METUPUK	Yes	Thank you for your comment. No action required.
	Breast Cancer Now	The outcome measures listed are appropriate	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Equality	AstraZeneca	AstraZeneca are not aware of any issues of inequality in the management of HR+/HER2- locally advanced or metastatic breast cancer in England and Wales.	Thank you for your comment. No action required.
	METUPUK	No comments	No action required.
	Breast Cancer Now	None that we would suggest	Thank you for your comment. No action required.
Other considerations	AstraZeneca	None	No action required.
	METUPUK	If genomic testing is required, will it be implemented alongside the PIK3CA testing already used in the NHS? Will prior treatment with fulvestrant be a barrier to accessing capivasertib with fulvestrant?	Thank you for your comment. The appraisal committee will take into consideration PIK3CA/AKT1/PTEN mutation testing costs in people who would not otherwise have been tested. No action required.
	Breast Cancer Now	We note that whilst PIK3CA is tested for, the other biomarkers mentioned may not be, so this additional testing may need to be a consideration.	Thank you for your comment. The appraisal committee will take into consideration PIK3CA/AKT1/PTEN mutation testing costs in people who would not

Section	Consultee/ Commentator	Comments [sic]	Action
			otherwise have been tested. No action required.
Questions for consultation	AstraZeneca	**Where do you consider capivasertib with fulvestrant will fit into the existing care pathway for hormone receptor-positive HER2-negative advanced breast cancer?** According to the proposed license wording, [redacted] We anticipate that capivasertib in combination with fulvestrant will be predominantly used after progression on first-line SoC with a CDK4/6i + AI regimen, and will displace the current second-line options: alpelisib with fulvestrant, and everolimus with exemestane. For a small proportion of endocrine -sensitive patients for whom CDK4/6i + AI treatment is not suitable and who therefore typically receive endocrine monotherapy in first-line, second-line options include further endocrine monotherapy or chemotherapy due to poor performance status, requirement for rapid disease control, or endocrine resistance. This population is different from the anticipated population of patients who will receive or capivasertib in combination with fulvestrant in practice [redacted] Therefore, capivasertib in combination with fulvestrant is not anticipated to displace use of further endocrine monotherapy or chemotherapy.	Thank you for your comments. Stakeholders can provide justification around the most appropriate comparators and the committee will consider this during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for capivasertib in combination with fulvestrant been included in the scope? In particular, are exemestane and tamoxifen appropriate comparators? All relevant comparators for capivasertib in combination with fulvestrant have been included in the scope. However, the following proposed comparators are not relevant: • Exemestane, tamoxifen, as well as other endocrine monotherapy options used for locally advanced or metastatic HR+/HER2- breast cancer are not deemed relevant comparators for this appraisal, as the patients who receive these monotherapies are not expected to be clinically suitable for combination endocrine therapies such as everolimus with exemestane, alpelisib with fulvestrant, or capivasertib in combination with fulvestrant (when available and reimbursed). • CDK4/6i + fulvestrant is also not considered an appropriate comparator for this appraisal as CDK4/6i + AI is regarded as the first-line SoC, and CDK4/6i re-challenge is not reimbursed in the UK Chemotherapy with or without endocrine therapy is also not regarded as an appropriate comparator for this appraisal as chemotherapy is typically reserved for patients who require rapid response, have visceral crisis, are endocrine-insensitive, and all other endocrine therapy options have been exhausted.	
	METUPUK	No comments	No action required.
	Breast Cancer Now	**Where do you consider capivasertib with fulvestrant will fit into the existing care pathway for hormone receptor-positive HER2-negative advanced breast cancer?**	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		In line with the clinical trial, we would expect capivasertib with fulvestrant to be used after treatment with an aromatase inhibitor with or without a CDK 4/6 inhibitor. **Have all relevant comparators for capivasertib with fulvestrant been included in the scope? In particular, are exemestane and tamoxifen appropriate comparators?** We will defer to clinical experts on this point. **Would capivasertib with fulvestrant be a candidate for managed access?** Potentially – overall survival data for this treatment does not appear to be available currently. We are not aware of current timelines for this. **Do you consider that the use of capivasertib with fulvestrant can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.**	
Additional comments on the draft scope	AstraZeneca	Based on clinician feedback, all patients who experience progression after first-line treatment for HR+/HER2- locally advanced or metastatic breast cancer are currently tested for the presence of PIK3CA alterations via the national genomic test directory commissioning route to assess their eligibility for alpelisib with fulvestrant. [redacted]	Thank you for your comment. The appraisal committee will take into consideration PIK3CA/AKT1/PTEN mutation testing costs in people who would not otherwise have been

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted]	tested. No action required.
	METUPUK	Patients value precision treatments over cytotoxic chemotherapy. We do not offer an opinion on where in the treatment cycle this drug should lie. We would welcome flexibility for oncologists to deploy capivasertib with fulvestrant according to the needs of their patient. PIK3CA mutations are tested for in this group of patients, and so adding AKT1 and PTEN to the diagnostics would be an important step towards personalised care. Capivasertib with fulvestrant could be a good candidate for managed access. More mature data could provide information on how the drug works over a longer timeframe. As a first in class AKT inhibitor a longer period of data collection is reasonable and would be valuable to the NHS. Patients often tell us that they prefer treatment targeted to their particular disease. Most patients would delay cytotoxic chemotherapy if they were offered effective alternatives because they have busy lives. This may be because they want to remain in employment or fulfil roles as carers for children or elderly relatives. Most importantly, they prefer a treatment which enables them to pursue interests and commitments which are important to them.	Thank you for your comment. No action required.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

Novartis