

MSAC Application 1766

Genetic testing to detect AKT-pathway alterations in patients with hormone receptor-positive, HER2-negative advanced breast cancer, to determine eligibility for PBS subsidised capivasertib treatment

PICO Set Document

Population

Describe the population in which the proposed health technology is intended to be used:

The application is to request public funding for the testing of AKT-pathway alterations (PI3KCA, AKT1 or PTEN) by Next Generation Sequencing (NGS) in tumour tissue from patients with locally advanced (inoperable) or metastatic HR-positive/HER2-negative (HR+/HER2-) breast cancer following recurrence or progression on or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor.

It is proposed to be a diagnostic service for eligibility for capivasertib + fulvestrant treatment in patients with confirmed AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour and locally advanced or metastatic HR+/HER2- breast cancer.

In CAPItello-291, the addition of capivasertib to fulvestrant significantly improved PFS in patients with AI-resistant HR+/HER2- advanced breast cancer in the overall population, with a more pronounced benefit in pathway altered tumours (Turner et al 2023).

Capivasertib is currently undergoing TGA evaluation for treatment in this population.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

Breast cancer is the most commonly diagnosed cancer among women in Australia, with approximately 57 Australians diagnosed each day, equating to over 20,000 Australians every year. (National Breast Cancer Foundation. 2021). Of those 20,000 Australians diagnosed with breast cancer each year, about 5% have metastatic breast cancer (Cancer Australia. 2019). Advanced breast cancer (ABC) comprises both locally advanced (inoperable) and metastatic disease. Although it can be treated, metastatic breast cancer remains incurable with a median survival of approximately 3 years and a 5-year survival rate of around 25% (Cardoso et al 2018). Several prognostic indicators for breast cancer have been identified including HER2 and ER/PR (here, also referred to as hormone receptor [HR]). Most of the improvements in survival rates achieved in the last decade have been due to advances in the treatment of patients with HER2+ tumours. Conversely, survival rates for patients with HR+/HER2- tumours, which account for approximately 70% of all breast cancers (Howlader et al 2014), have not shown much improvement over the same period (Gobbini et al 2018).

In the majority of cases, endocrine-based therapy is the initial treatment for HR+/HER2- breast cancer. The exceptions are patients with visceral crisis or in whom endocrine-based alternatives have been exhausted or for whom there is evidence of endocrine resistance; in such instances, chemotherapy is required.

Many patients with HR+/HER2- breast cancer benefit from sequential use of endocrine therapies and those who respond to endocrine therapy with either tumour shrinkage or long-term stabilisation (i.e., clinical benefit) should be offered additional endocrine therapy at subsequent disease progression (Telli et al 2019) to maintain disease control. The optimal sequence and integration of the available endocrine agents is not established and is influenced by choice of initial therapy, the response obtained, as well as individual patient and disease characteristics (Cardoso et al 2018).

Several novel, effective agents have become available in recent years for combination with endocrine therapies. In particular for Australia, these include cyclin-dependent kinase (CDK) 4/6 inhibitors which have become standard of care in 1L metastatic breast cancer. Alternatively, everolimus in combination with exemestane (an inhibitor of the mammalian target of the rapamycin receptor [mTOR]) however, it is not used much in Australia due to minimal magnitude of benefit in real world treatments after progression on 1L CDK4/6-inhibitors. Available second or further lines of therapies are limited either with regard to the population able to gain benefit, or the minimal magnitude of benefit (Cardoso et al 2018).

More recently, the Phase III SOLAR-1 study demonstrated an improvement in PFS of 5.7 to 11 months with the addition of the alpha-specific PI3K inhibitor alpelisib to fulvestrant in patients with HR+/HER2- advanced breast cancer with tumours harbouring a PIK3CA mutation, who had relapsed or progressed on an AI (André et al 2019), based on which the FDA granted approval. Despite these advances, these tumours eventually develop endocrine resistance necessitating the use of chemotherapy and thus, HR+/HER2- advanced breast cancer remains an area of considerable unmet medical need, especially post-CDK4/6-inhibitor use.

The AKT serine/threonine protein kinases (AKT1, AKT2, AKT3) are key downstream effectors of the PI3K/AKT/mTOR pathway, mediating cell proliferation and resistance to apoptosis, and are activated in a wide range of solid and haematologic malignancies (Brown et al 2017, Lindsley et al 2010, Liu et al 2019). AKT activation in tumours is largely due to input from other signalling pathways upstream of AKT including loss of PTEN function and activating mutations in the catalytic subunit of PI3K (PIK3CA) (Yi et al 2016).

Numerous preclinical studies show that endogenous AKT activity promotes breast cancer cell survival and resistance to chemotherapy or endocrine therapy (Frogne et al 2005, Ghayad et al 2010, van der Hage et al 2004). This can be overcome by down-regulation or inhibition of the PI3K/AKT pathway, as it has been shown in several *in vitro* and *in vivo* breast cancer models (Frogne et al 2005, Ghayad et al 2010, van der Hage et al 2004).

Capivasertib is under investigation by AstraZeneca for a range of therapeutic indications (Banerji et al 2018, Tamura et al 2016) including triple-negative breast cancer (TNBC), ER+/HER2- breast cancer and prostate cancer. Capivasertib inhibits the proliferation of 25 out of 180 tumour cell lines with a concentration causing 50% inhibition of cell growth (GI50) of <1 µM. Breast cancer cell lines show the highest frequency of sensitivity to capivasertib, with a significant correlation between the presence of PIK3CA or PTEN mutations and sensitivity (Davies et al 2012). Capivasertib inhibits the growth of several human breast cancer xenograft models, including the TNBC xenograft model HCC1187 and the HER2+, PIK3CA mutant xenograft models BT474 and HCC1954.

In CAPItello-291, the addition of capivasertib to fulvestrant significantly improved PFS in patients with AI-resistant HR+/HER2- advanced breast cancer in the overall population, with a more pronounced benefit in pathway altered tumours (Turner et al 2023).

Capivasertib is currently undergoing TGA evaluation for treatment in this population.

Provide a rationale for the specifics of the eligible population:

For locally advanced, recurrent breast cancer, the goal is long-term survival. For metastatic BC, goals include prolonging life, improving quality of life, shrinking or slowing the growth of tumours. For 1L treatment of HR+ recurrent unresectable breast cancer or mBC, the ESMO Guidelines recommend combination therapy of endocrine therapy with a CDK4/6 inhibitor (plus

ovarian suppression for premenopausal or perimenopausal patients). If organ failure is imminent, chemotherapy is recommended as 1L treatment. For 2L+ treatment of HR+ recurrent unresectable breast cancer or mBC, the ESMO Guidelines recommend endocrine therapy with or without a CDK4/6 inhibitor, PI3K inhibitor, or mTOR inhibitor; a PARP inhibitor, if BRCA/PALB2 mutations are present; and, if there is imminent organ failure or short PFS on endocrine-based therapy, sacituzumab govitecan if HER2-negative or trastuzumab deruxtecan if HER2-low (IHC 1+ or IHC 2+/ISH-negative) breast cancer.

A key unmet need for 2L treatment of HR+ recurrent unresectable breast cancer or mBC is to develop better endocrine therapy-based options with a tolerable safety profiles and wide therapeutic windows, before the tumour becomes endocrine refractory.

The AKT serine/threonine protein kinases (AKT1, AKT2, AKT3) are key downstream effectors of the PI3K/AKT/mTOR pathway, mediating cell proliferation and resistance to apoptosis, and are activated in a wide range of solid and haematologic malignancies (Brown and Banerji 2017, Lindsley 2010, Liu et al 2019). AKT activation in tumours is largely due to input from other signalling pathways upstream of AKT including loss of PTEN function and activating mutations in the catalytic subunit of PI3K (PIK3CA) (Yi and Lauring 2016).

Numerous preclinical studies show that endogenous AKT activity promotes breast cancer cell survival and resistance to chemotherapy or endocrine therapy (Frogne et al 2005, Ghayad et al 2010, van der Hage et al 2004). This can be overcome by down-regulation or inhibition of the PI3K/AKT pathway, as shown in several *in vitro* and *in vivo* breast cancer models (Frogne et al 2005, Ghayad et al 2010, van der Hage et al 2004).

Thus, the proposed medical service is testing for AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumours in patients with HR-positive, HER2-negative advanced or inoperable metastatic breast cancer.

Are there any prerequisite tests?

No

Are the prerequisite tests MBS funded?

No

Please provide details to fund the prerequisite tests:

HR+/HER2- recurrent, unresectable, or metastatic breast cancer who have relapsed on endocrine therapy. One of the mechanisms of resistance to endocrine therapy is the activation of the AKT Pathway (PIK3CA/AKT/PTEN), a signalling pathway causing tumour growth, and relapse of disease. AKT Pathways activation includes:

- Activating mutations in PIK3CA or AKT1 which can inappropriately activate the pathway.
- Loss of function mutations in PTEN which can lead to unregulated signalling.

Testing for these resistant mutations is not currently routinely performed.

The proposed new test will be conducted on the tumour tissue sample and performed by a molecular pathologist and a registered anatomical pathologist in an accredited laboratory.

AZ proposes a new MBS item descriptor below:

Table 1 Requested new MBS item descriptor

| | | |
|--|---------------------|---------------------------------|
| | | Category 6 – Pathology Services |
| MBS item XXXX | | Group P7 – Genetics |
| <p>A test of tumour tissue for the detection of an AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour, in a patient with:</p> <ul style="list-style-type: none"> locally advanced (inoperable) or metastatic hormone receptor positive, HER2-negative breast cancer <p>As requested by a specialist or consultant physician, to determine eligibility for treatment with an AKT serine/threonine kinase - inhibitor under the Pharmaceutical Benefits Scheme (PBS)</p> | | |
| Fee: \$XX | Benefit: 75% = \$XX | 85% = \$XX |

Intervention

Name of the proposed health technology:

Testing for AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumours in patients with HR-positive, HER2-negative advanced or inoperable metastatic breast cancer to determine eligibility for treatment with capivasertib, an AKT inhibitor, in combination with fulvestrant, to inhibit both ER signalling and its interactions with the PIK3CA/AKT1/PTEN pathway.

The addition of capivasertib to fulvestrant significantly improved PFS in patients with AI-resistant HR+/HER2– advanced breast cancer in the overall population, with a more pronounced benefit in pathway altered tumours (Turner et al 2023).

Capivasertib is currently undergoing TGA evaluation for treatment in this population.

Describe the key components and clinical steps involved in delivering the proposed health technology:

Identification of AKT-pathway alterations (PIK3CA, AKT1 or PTEN) using NGS in tumour tissue from patients with HR+/HER2- advanced breast cancer. NGS enables the identification of hundreds of genes at one time and can identify mutations such as PIK3CA, ATK1 & PTEN.

Using NGS, the pathologist will be able to preselect the genes to identify - they often referred to this as a 'A Testing Panel', in this case, a 'Breast Panel' will be used to identify PIK3CA, ATK1 or PTEN. This test will confirm AKT-pathway altered tumours with known PIK3CA, AKT1 or PTEN mutations.

Identify how the proposed technology achieves the intended patient outcomes:

The application requests public funding for the testing of AKT-pathway alterations (PIK3CA, AKT1 or PTEN) using an NGS panel as a diagnostic service to determine eligibility for capivasertib in combination with fulvestrant treatment in patients with locally advanced (inoperable) or metastatic HR-positive, HER2-negative breast cancer following recurrence or progression on or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor.

The addition of capivasertib to fulvestrant significantly improved PFS in patients with AI-resistant HR+/HER2– advanced breast cancer in the overall population, with a more pronounced benefit in pathway altered tumours (Turner et al 2023).

Capivasertib is currently undergoing TGA evaluation for treatment in this population.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

No

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

N/A

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

No

Provide details and explain:

If AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour retesting is deemed necessary to verify AKT-pathway altered status prior to capivasertib treatment, the proposed testing, interpretation and reporting paradigm will remain unchanged as systems are already in place to report on the diagnostic criteria required to identify patients with this disease phenotype.

Where a tissue sample is not readily available (i.e., fresh tissue [e.g., based on the site of local recurrence or metastasis], or there is no archival tissue), the test could potentially be performed on a plasma sample. Once plasma sample ctDNA becomes more routinely available and conducted in clinical practice, it can be requested by a surgeon, oncologist or general practitioner, or ordered by these practitioners and taken at a laboratory. Analysis of the ctDNA in the plasma sample is performed in a similar way to the tissue sample.

Noting the challenges with biopsies outlined previously, with the availability of capivasertib, re-testing and/or re-biopsy rates may increase but given the small number of patients the impact to the MBS is likely to be small.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

A registered molecular pathologist and a registered anatomical pathologist are responsible for conducting the detection, diagnosis and reporting of the pathology result to help guide and determine treatment.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

A registered anatomical pathologist is responsible for conducting the detection, diagnosis and reporting of the pathology results which guide and determine treatment. A specialist (e.g., medical oncologist, breast surgeon, interventional radiologist) provides the specimen and a test request form for testing.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

Provide details and explain:

Training and qualifications for laboratory personnel performing the AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour NGS test would be the same as those required for laboratory personnel currently performing other cancer biomarker testing. Pathology laboratories performing NGS testing would need to be NATA-accredited, and as per other cancer biomarker tests, competence in AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour NGS testing would be monitored via a Quality Assurance Program (QAP) by the Royal College of Pathologists of Australia (RCPA).

Indicate the proposed setting(s) in which the proposed health technology will be delivered:

- Consulting rooms
- Day surgery centre
- Emergency Department
- Inpatient private hospital
- Inpatient public hospital
- Laboratory
- Outpatient clinic
- Patient's home
- Point of care testing
- Residential aged care facility
- Other (please specify)

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:

N/A

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

The nominated comparator is no test.

List any existing MBS item numbers that are relevant for the nominated comparators:

N/A

Please provide a rationale for why this is a comparator:

Currently for patients with AKT-pathway altered (PIK3CA, AKT1, PTEN) tumour and HR-positive, HER2-negative advanced breast cancer, treatments are not targeted so typically involve alternative therapeutic agents that a patient has not been exposed to.

For 1L treatment of HR+ recurrent unresectable breast cancer or mBC, the ESMO Guidelines recommend combination therapy of endocrine therapy with a CDK4/6 inhibitor (plus ovarian suppression for premenopausal or perimenopausal patients). If imminent organ failure, chemotherapy is recommended as 1L treatment. For 2L+ treatment of HR+ recurrent unresectable breast cancer or mBC, the ESMO Guidelines recommend endocrine therapy with or

without a CDK4/6 inhibitor, PI3K inhibitor, or mTOR inhibitor; a PARP inhibitor, if BRCA/PALB2 mutations are present; and, if there is imminent organ failure or short PFS on endocrine-based therapy, sacituzumab govitecan if HER2-negative or trastuzumab deruxtecan if HER2-low (IHC 1+ or IHC 2+/ISH-negative) breast cancer.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

- None – used with the comparator
- Displaced – comparator will likely be used following the proposed technology in some patients
- Partial – in some cases, the proposed technology will replace the use of the comparator, but not all
- Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

There is no comparator

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

- Health benefits
- Health harms
- Resources
- Value of knowing

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

In the CAPItello-291 trial, the addition of capivasertib to fulvestrant treatment led to a significant improvement, in progression-free survival among patients with AKT-pathway altered (PIK3CA, AKT1, or PTEN) tumours and hormone receptor– positive, advanced breast cancer who had disease progression during or after previous endocrine therapy, with or without a CDK4/6 inhibitor, when compared to treatment with fulvestrant alone.

Proposed MBS items

How is the technology/service funded at present? (for example: research funding; State-based funding; self-funded by patients; no funding or payments):

Currently, in Australia the AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour test is privately funded by patients

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention:

Proposed item details

| | |
|---|--|
| MBS item number | N/A |
| Category number | Category 6 – Pathology Services |
| Category description | Group P7 – Genetics |
| Proposed item descriptor | A test of tumour tissue for the detection of an AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumour, in a patient with: <ul style="list-style-type: none"> locally advanced (inoperable) or metastatic hormone receptor positive, HER2-negative breast cancer As requested by a specialist or consultant physician, to determine eligibility for treatment with an AKT serine/threonine kinase - inhibitor under the Pharmaceutical Benefits Scheme (PBS) |
| Proposed MBS fee | The proposed MBS fee is currently unavailable |
| Indicate the overall cost per patient of providing the proposed health technology | A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission. |
| Please specify any anticipated out of pocket expenses | A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission. |
| Provide any further details and explain | A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission. |

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

The current key components and clinical steps involved in delivering a tumour genetic mutation test in patients with HR-positive/HER2-negative breast cancer are as follows:

Patient's tumour sample is taken and sent to a pathology laboratory where testing for AKT-pathway alterations (PIK3CA, AKT1 or PTEN) is performed. Tumour tissue specimens for testing for the target patient population may be obtained as either a fresh tissue from the recurrent disease, or from tissue specimen as formalin-fixed paraffin-embedded (FFPE) blocks following primary tumour debulking surgery.

1. Macro- or micro-dissection of the specimen may be required to increase the proportion of tumour tissue. DNA is extracted, purified and may be quantified using the laboratory's preferred commercially available kits. PCR amplification methods, including multiplex ligation dependent probe amplification (MLPA) may be used. Hybridisation capture baits may also be used. Libraries for sequencing are prepared and library quality may be evaluated at this step. Some gene panels (e.g., PIK3CA, AKT1 or PTEN) identify all classes of mutations including single base substitutions, small insertions and deletions and large gene re-arrangements. Variants are called using comparison to reference libraries. Next-generation sequencing (NGS) is performed at most Australian laboratories using a range or number of NGS platforms. Sequencing results are then reported to the requesting specialist or consultant physician.

2. Based on a positive AKT-pathway alteration/s (PIK3CA, AKT1 or PTEN) test result, the medical practitioner will consider prescribing capivasertib + fulvestrant to the patient if they meet the PBS criteria to access treatment.

Where a tissue sample is not readily available (i.e., fresh tissue [e.g. based on the site of local recurrence or metastasis], or there is no archival tissue), testing could potentially be performed on a plasma sample. Once plasma sample ctDNA becomes more routinely available and conducted in clinical practice, it can be requested by a surgeon, oncologist or general practitioner, or ordered by these practitioners and taken at a laboratory. Analysis of the ctDNA in the plasma sample is performed in a similar way to the tissue sample.

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

Yes

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

Currently for patients with AKT-pathway altered (PIK3CA, AKT1, PTEN) tumour and HR-positive, HER2-negative advanced breast cancer, treatments are not targeted so typically involve alternative therapeutic agents that a patient has not been exposed to.

Patients with confirmed AKT-pathway alteration may be eligible for capivasertib treatment.

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Tumour tissue specimens for testing for the target patient population may be obtained as either a fresh tissue from the recurrent disease, or from tissue specimen from primary tumour debulking surgery to perform an AKT-pathway altered tumour test. This is part of the standard diagnostic process, and some biomarker tests are funded via the MBS. With the availability of targeted therapies from first-line therapy, it is anticipated that there may be a small increase in the extent of biopsies, with a minimal additional budget impact.

Explain what other healthcare resources are used in conjunction with the comparator health technology:

The current comparator is no comparator.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Re-testing and/or re-biopsy may be required for some patients.

In the CAPitello-291, there was a small population that did not have a viable tumour tissue sample at disease progression. These patients may be required to re-biopsy if a viable tumour tissue sample is available after disease progression, or they may benefit from a ctDNA test which may become routinely conducted in clinical practice.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

A clinical management algorithm is provided below.

The addition of capivasertib to fulvestrant significantly improved PFS in patients with AI-resistant HR+/HER2- advanced breast cancer in the overall population, with a more pronounced benefit in AKT-pathway altered tumours (Turner et al 2023).

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

Patients diagnosed with HR+/HER2- breast cancer generally initially receive endocrine therapy such as tamoxifen or an aromatase inhibitor. Initial endocrine therapy may have been in the adjuvant setting, or as first-line therapy for *de novo* advanced breast cancer. More recently, a CDK inhibitor may be used in combination with the non-steroidal aromatase inhibitor in the advanced breast cancer setting.

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

As shown in the clinical algorithm below, there are a number of treatment options available in the second-line setting. Patients may subsequently move between these treatment options for later lines of therapy, including moving to best supportive care.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

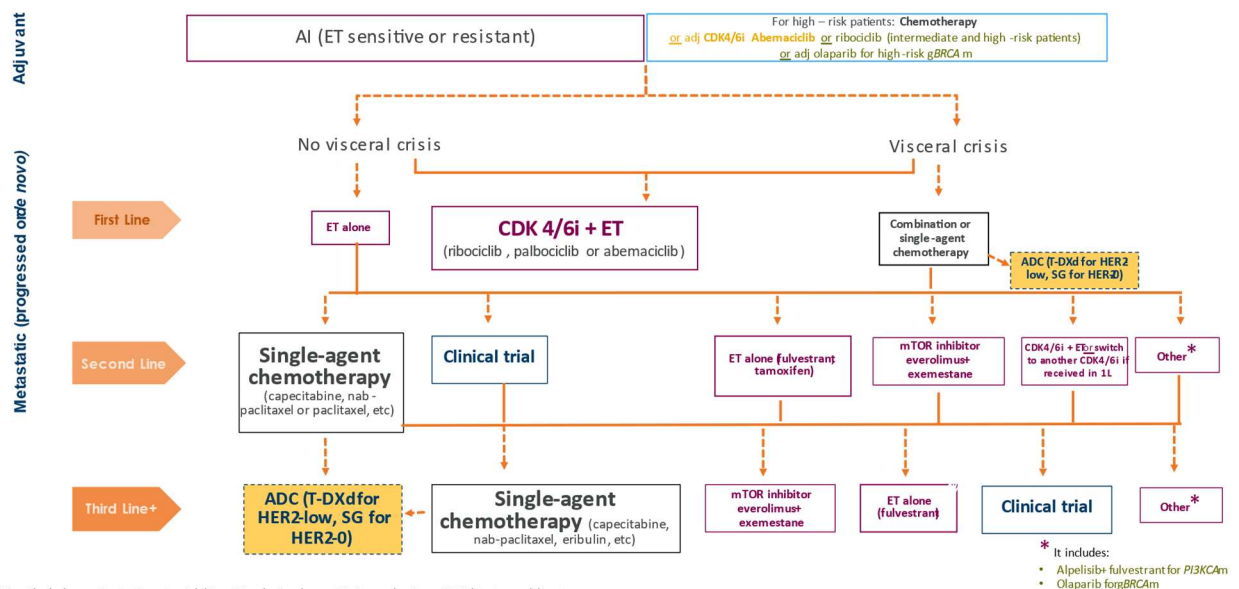


Figure 1: Current treatment algorithm in patients with HR+/HER2- breast cancer

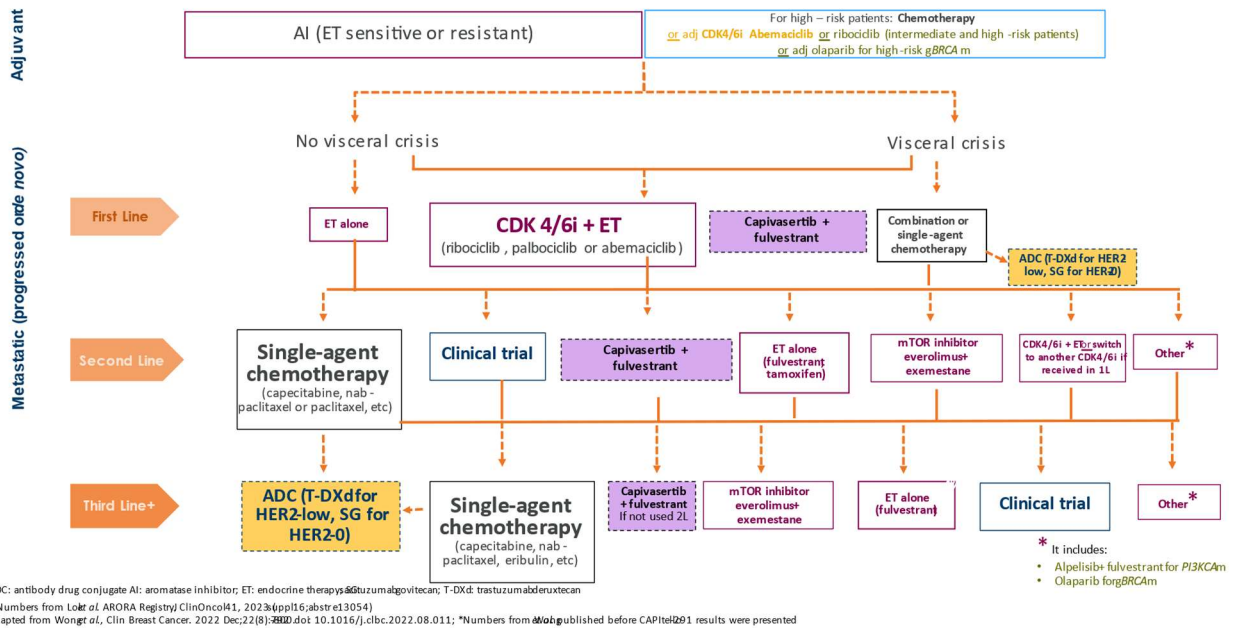


Figure 2: Revised treatment algorithm in patients with HR+/HER2- breast cancer (capiasertib)

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

- Superior
 Non-inferior
 Inferior

Please state what the overall claim is, and provide a rationale:

Superiority vs. No testing + standard of care therapy

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

This application requests public funding for AKT-pathway altered (PIK3CA, AKT1 or PTEN) tumours to be included in an NGS panel as a diagnostic service to determine eligibility for capivasertib in combination with fulvestrant treatment for patients with locally advanced (inoperable) or metastatic HR+/HER2- breast cancer following recurrence or progression on or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor.

In the CAPtello-291, there was a small population that did not have a viable tumour tissue sample at disease progression. These patients may be required to re-biopsy if a viable tumour tissue sample is available after disease progression or they may benefit from a ctDNA test which may become routinely conducted in clinical practice.

Identify how the proposed technology achieves the intended patient outcomes:

In the CAPItello-291 trial, the addition of capivasertib to fulvestrant treatment led to a significant improvement, in progression-free survival among patients with AKT pathway altered (PIK3CA, AKT1 or PTEN) tumours and hormone receptor– positive, advanced breast cancer who had disease progression during or after previous endocrine therapy, with or without a CDK4/6 inhibitor, compared to treatment with fulvestrant alone. Diarrhoea and rash were the main adverse events in patients treated with capivasertib + fulvestrant.

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?

Yes

A change in health outcome?

Yes

Other benefits?

No

Please provide a rationale, and information on other benefits if relevant:

N/A

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator? (please select your response)

- More costly
- Same cost
- Less costly

Provide a brief rationale for the claim:

The listing of capivasertib on the PBS may impact the utilisation of biopsy for the testing of tumour tissue for AKT-pathway alterations using NGS technology.

A detailed utilisation analysis will be presented in the integrated co-dependent MSAC/PBAC submission.

Summary of Evidence

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary (repeat columns as required).

| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|----|--------------------------|--|--|---|---------------------|
| 1. | Phase III Clinical trial | Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer | <p>Randomised, double blind, clinical trial in HR+/HER2- ABC. Patients treated with capivasertib+fulvestrant vs placebo + fulvestrant.</p> <p>Capivasertib+fulvestrant therapy resulted in significantly longer PFS than treatment with fulvestrant alone among patients with HR+/HER2- ABC whose disease had progressed during or after previous AI therapy with or without a CDK4/6 inhibitor</p> | https://www.nejm.org/doi/full/10.1056/NEJMoa2214131 | June 2023 |
| 2. | Review | Maximising the potential of AKT inhibitors as anti-cancer treatments | <p>PIK3CA/AKT signalling is commonly disrupted in human cancers, with AKT being a central component of the pathway, influencing multiple processes that are directly involved in tumourigenesis. Targeting AKT is therefore a highly attractive anti-cancer strategy with multiple AKT inhibitors now in various stages of clinical development.</p> <p>In this review, we summarise the role and regulation of AKT signalling in normal cellular physiology. We highlight the mechanisms by which AKT signalling can be hyperactivated in cancers and discuss the past, present and future clinical strategies for AKT inhibition in oncology</p> | https://www.sciencedirect.com/science/article/pii/S0163725816302443 | April 2017 |

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| | Type of study design | Title of journal article or research project | Short description of research | Website link to journal article or research | Date of publication |
|----|-----------------------------|---|---|---|----------------------------|
| 3. | Review | The Akt/PKB Family of Protein Kinases: A Review of Small Molecule Inhibitors and Progress Towards Target Validation: A 2009 Update | AKT plays a pivotal role in cell survival and proliferation through a number of downstream effectors. Recent studies indicate that unregulated activation of the PIK3CA/AKT pathway is a prominent feature of many human cancers and AKT is over-expressed or activated in all major cancers | https://www.ingentaconnect.com/content/ben/ctmc/2010/00000010/00000004/art00007 | March 2010 |
| 4. | Review | Targeting the phosphoinositide 3-kinase pathway in cancer | The phosphoinositide 3-kinase (PIK3CA) pathway is a key signal transduction system that links oncogenes and multiple receptor classes to many essential cellular functions, and is perhaps the most commonly activated signalling pathway in human cancer. This pathway therefore presents both an opportunity and a challenge for cancer therapy. Even as inhibitors that target PI3K isoforms and other major nodes in the pathway, including AKT and mammalian target of rapamycin (mTOR), reach clinical trials, major issues remain. | https://www.nature.com/articles/nrd2926 | August 2009 |
| 5. | Review | Preclinical Pharmacology of AZD5363, an Inhibitor of AKT: Pharmacodynamics, Antitumor Activity, and Correlation of Monotherapy Activity with Genetic Background | AKT is a key node in the most frequently deregulated signaling network in human cancer. AZD5363, a novel pyrrolopyrimidine-derived compound, inhibited all AKT isoforms with a potency of 10 nmol/L or less and inhibited phosphorylation of AKT substrates in cells with a potency of approximately 0.3 to 0.8 µmol/L. | https://aacrjournals.org/mct/article/11/4/873/91239/Pre-clinical-Pharmacology-of-AZD5363-an-Inhibitor | April 2012 |

References

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- Australian Government, Cancer Australia. 2019. Top 10 best practices for people with metastatic breast cancer. Available at: <https://www.canceraustralia.gov.au/about-us/news/top-10-best-practices-people-metastatic-breast-cancer>. [Accessed August 2021]
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