MSAC Application 1816

Genetic testing to detect estrogen receptor 1 (ESR1) variants in patients with hormone receptor (HR)-positive, HER-2 negative, locally advanced or metastatic breast cancer to determine eligibility for treatment with PBS subsidised camizestrant

PICO Set

Population

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

Patients with newly diagnosed locally advanced or metastatic HR-positive, HER2-negative breast cancer who have received first line treatment with a CDK4/6 inhibitor in combination with an aromatase inhibitor (AI), for at least 6 months, and whose disease has not progressed clinically or radiographically.

The application is to request public funding for the testing of *ESR1* mutations in ctDNA extracted from blood (liquid biopsy) from patients with newly diagnosed locally advanced or metastatic HR-positive, HER2-negative breast cancer who have received first line treatment with a CDK4/6 inhibitor in combination with an aromatase inhibitor for at least 6 months, and who disease has not progressed clinically or radiographically.

Patients who are test positive for *ESR1* mutations, may be eligible to switch from the current AI to PBS subsidised camizestrant, a novel selective oestrogen receptor degrader (SERD), in combination with the CDK4/6 inhibitor they are already receiving.

Camizestrant is currently undergoing TGA evaluation in this patient population. The proposed indication wording is:

Advanced breast cancer upon emergence of ESR1 mutation during first-line endocrine-based therapy

Camizestrant in combination with a CDK4/6 inhibitor is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer upon emergence of ESR1 mutation during first-line endocrine-based therapy.

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 (BC) is the most commonly diagnosed cancer among women in Australia. There were 21,194 patients diagnosed in 2024 and 3,305 deaths from the disease (AIHW, 2024). Advanced BC comprises both locally advanced (inoperable) and metastatic disease, referred hereon collectively as mBC.

Due to funded breast cancer screening programs and education on self-examination, approximately 80% of BC is diagnosed in Stages I-II before disease has spread (AIHW 2024). Being diagnosed earlier results in a more favourable prognosis where 5-year survival for patients with Stage I BC is 100% and Stage II is 94.6% (AIHW 2024). Patients diagnosed in the advanced stages of the disease, when the tumour has spread significantly within the breast or to other organs in the body, have lower 5-year survival rates, 80.6% for Stage III, dropping dramatically to 32% for Stage IV patients (AIHW 2024). Approximately 30% of patients diagnosed with early BC (eBC) will subsequently develop either a local recurrence or metastatic disease (Redig et al 2013).

Several prognostic indicators for BC have been identified including HER2, ER and progesterone receptor (PR) (ER and PR are also collectively referred to as hormone receptors [HR]). The most common subtype is ER-positive, HER2-negative, accounting for about 70% of cases of BC (Howlader, et al., 2014; Iwase, et al., 2021; Anderson, et al., 2017; Zhou, et al., 2023).

The standard of care (SoC) for the first line treatment of HR-positive, HER2-negative mBC is the combination of a CDK4/6 inhibitor with an AI until disease progression. All tumours will eventually develop resistance to endocrine therapies and *ESR1* mutations represent a type of acquired resistance in up to 40-50% of patients after initial ET in the metastatic setting (Brett et al 2021; Santiago Novello et al 2023). *ESR1*-mutations alter the conformation of the ER ligand binding domain that results in ligand independent ER activation and constitutive ER signalling that promotes tumour growth and resistance, predominantly after ET (Brett et al 2021; Santiago Novello et al 2023; Lin et al 2023; Bhave et al 2023; Toy et al 2013). Once patients progress on 1L therapy, the subsequent endocrine based therapies have limited efficacy, and patients will eventfully require treatment with chemotherapy. Disease progression and the use of chemotherapy are associated with a deterioration in quality of life (Giuliano et al 2019), underscoring the need to continue to improve 1L treatments, to keep patients free of disease progression for as long as possible.

The PlasmaMATCH study (Turner et al 2020) showed fulvestrant, an intramuscular injected selective oestrogen receptor downgrader (SERD) has very limited activity in patients who are *ESR1*m-positive even with higher than current standard doses. Of note, all of the partial responses observed in the *ESR1*m positive cohort were in patients where a dominant *ESR1*m was detected in their circulating DNA (ctDNA), not in patients with multiple *ESR1*m. This is consistent with the hypothesis that patients with a more genetically diverse tumour burden are more likely to be resistant to intervention with a SERD and that early intervention, before too much genetic drift has occurred, may be advantageous i.e. switching from AI to a SERD before disease progression has occurred.

Evidence suggests that detection of *ESR1*m is associated with poor treatment outcomes in terms of progression-free survival (PFS) and overall survival (OS) (Turner et al 2020), mainly owing to a lack of effective treatment options to address this driver mutation. Elacestrant is currently being evaluated by the TGA and is the first treatment targeting *ESR1*m, in patients with *ESR1*m after disease progression following at least one line of ET. As monotherapy in the post-CDK4/6 inhibitor treatment setting, the treatment effect is modest, with a median PFS of 3.8 months for elacestrant vs 1.9 months for fulvestrant (Shah et al 2024).

The advent of highly sensitive ctDNA technology allows early detection of emerging endocrine therapy resistance mutations (during first line treatment) before radiologic or clinical disease progression has occurred. Switching from an AI to camizestrant at this early stage, ahead of disease progression, to target *ESR1* mutation clonal expansion, has the potential to restore endocrine sensitivity and extend the duration patients remain free from progressive disease.

Camizestrant is an oral next generation SERD (ngSERD) and complete ER antagonist. Camizestrant binds to the ligand binding domain of ERα, antagonising the activity of ERα encoded by both wild-type *ESR1* and mutated *ESR1*, and inducing proteasome-dependent degradation of ERα, without agonising ERα.

An early switch of the ET backbone from AI to camizestrant in patients on first line treatment with a CDK4/6 inhibitor, upon emergence of *ESR1*m, has been shown in the phase 3 randomised controlled trial, SERENA-6, to prolong the benefit of first line therapy. This approach effectively suppresses and delays the resistance to treatment that ultimately leads to clinical disease

progression and decline in quality of life (QoL). Extending the duration of benefit on first line therapy translates into better patient outcomes, addressing this important and high unmet medical need.

Patients who would be considered eligible for *ESR1*m testing, are patients with newly diagnosed HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received treatment with a CDK4/6 inhibitor in combination with an AI, for at least 6 months, and whose disease has not progressed clinically or radiographically. The *ESR1*m testing would be requested by the treating clinician (most likely a medical oncologist) and the blood taken to enable the test likely to be completed at the same time as other routine blood monitoring (up to 6 times per year).

Provide a rationale for the specifics of the eligible population:

For patients with locally advanced or metastatic BC, the treatment goals are extending time spent free of disease progression, prolonging overall survival and improving or at a minimum, not negatively impacting quality of life. International treatment guidelines recommend the requested population be treated with a CDK4/6 inhibitor in combination with an AI. If organ failure is imminent, chemotherapy is recommended.

As described above, all patients will develop endocrine resistance to ET and *ESR1*m represent a type of acquired resistance in up to 40-50% of patients after initial ET in the metastatic setting (Brett et al 2021; Santiago Novello et al 2023). Once patients progress on first line therapy, the subsequent endocrine based therapies have limited efficacy, and patients will eventfully require treatment with chemotherapy. Disease progression and the use of chemotherapy are associated with a deterioration in quality of life (Giuliano et al 2019), underscoring the need to continue to improve first line treatments, to keep patients free of disease progression for as long as possible.

Sadly, many patients will not go on to receive second line treatment for their disease. Currently available second line treatments including SERD as monotherapy provide suboptimal efficacy and limited progression free survival (PFS) outcomes. The limited benefit of second line treatments highlights the need for durable first line treatment options.

Switching from AI to camizestrant following detection of an *ESR1*m, and continuing the CDK4/6 inhibitor, provides patients with an average of almost 7 months of additional time spent free of disease progression.

Intervention

Name of the proposed health technology:

Testing for *ESR1* mutations in ctDNA via liquid biopsy in patients with HR-positive, HER2-negative locally advanced or metastatic BC who have received at least 6 months of treatment with a CDK4/6 inhibitor in combination with an AI and whose disease has not yet progressed clinically or radiographically, to determine eligibility for PBS-funded treatment with camizestrant in combination with the same CDK4/6 inhibitor they are already receiving.

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

Identification of *ESR1* mutations in ctDNA via liquid biopsy using either digital PCR (dPCR) or Next Generation Sequencing (NGS). The concordance studies currently underway will determine which methodology is recommended in the co-dependent submission.

Identify how the proposed technology achieves the intended patient outcomes:

The proposed technology (*ESR1*m testing) will identify patients who are mutation positive to determine eligibility for PBS-funded treatment with camizestrant, while continuing the CDK4/6 inhibitor. This applies to patients with newly diagnosed locally advanced or metastatic HR-positive, HER2-negative BC, who have received first line treatment with a CDK4/6 inhibitor in combination with an AI, for at least 6 months, and whose disease develops molecular resistance to AI (detected by *ESR1*m) without clinical or radiographic progression.

The SERENA-6 trial demonstrates the clinical utility of testing ctDNA for emerging *ESR1*m and switching from AI to camizestrant: an average of almost 7 months gain in PFS (HR 0.44 95% CI .31-0.60, $p<0.00001$) in this patient population (Bidard et al 2025). Further, patients switched to camizestrant, experienced a reduced risk of deterioration in patient reported overall health and QoL and reduction in several symptom and function domains: pain, shortness of breath/dyspnoea, breast and arm symptoms; and physical, role and emotional functions, compared with continuing the current standard of care, AI in combination with CDK4/6 inhibitor (Bidard et al 2025; Mayer et al 2025).

Camizestrant is currently undergoing TGA evaluation for treatment in this patient 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:

NA

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:

Due to the design of the SERENA-6 trial, where patients were tested for *ESR1*m every 2-3 months (coinciding with routine clinical assessments), whilst remaining free of disease progression, the proposed *ESR1*m test may be requested more than once per patient. In SERENA-6, an *ESR1*m was detected by the first test in 51% of the patients. In subsequent tests, between the second to the fifth test, *ESR1*m was detected in 38% of the patients, and about 11% of the patients demonstrated *ESR1*m after the fifth test (Turner et al 2025, presented at ASCO). Further details on the number of tests administered in the trial and what is expected to happen in practice will be presented in the integrated co-dependent submission.

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:

NA

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 referral for blood collection 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 *ESR1*m ctDNA dPCR and/or NGS tests would be the same as those required for laboratory personnel currently performing other cancer biomarker testing. Pathology laboratories performing testing would need to be NATA-accredited, and as per other cancer biomarker tests, competence in ctDNA dPCR/NGS testing would be monitored via a Quality Assurance Program (QAP) by the Royal College of Pathologists of Australia (RCPA).

Special training (education and awareness) from the pathology laboratories maybe required at collection centres to ensure that blood samples are collected and transported in special tubes that are suitable sample stability and for subsequent ctDNA testing.

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)

Specify further details here

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:

NA

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:

Please provide a name for your comparator:

No testing

Please provide an identifying number for your comparator (if applicable):

NA

Please provide a rationale for why this is a comparator:

Patients are not currently tested for *ESR1*m because there are currently no *ESR1*m targeted therapies listed on the PBS.

AstraZeneca notes MSAC did not recommend the recent Application 1782, requesting reimbursement of *ESR1*m testing in HR-positive, HER2-negative mBC patients, but from the start of second line treatment. This application did request patients could be re-tested. At the time of the submission of this application, AstraZeneca was not aware of any re-submission of Application 1782.

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? (please select your response)

☒ 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 in all cases
☐ 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 test as the 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

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

In the SERENA-6 trial, the switch from AI to camizestrant (in combination with the existing CDK 4/6 inhibitor) upon detection of *ESR1*m and ahead of disease progression, extended the duration of benefit of first line treatment in patients whose disease developed molecular resistance to AI and substantially delayed disease progression. Patients experienced a highly clinically and statistically significant improvement in investigator assessed PFS: mPFS 15.97 months compared to 9.23 months (HR 0.44; 95% CI, 0.31-0.60, p<0.00001). Analysis of PFS according to blinded independent central review was also consistent with the primary analysis (HR: 0.43; 95% CI: 0.29–0.63; median 19.3 months vs 11.5 month; Bidard et al 2025). Patients receiving camizestrant also experienced a significant reduced risk of deterioration in patient-reported cancer symptoms (pain, shortness of breath/dyspnoea, breast and arm symptoms) and functioning (physical, role and emotional) compared with the current standard of care, AI in combination with CDK4/6 inhibitor (Mayer et al 2025).

The most common adverse event of any grade was neutropenia (54.8% in the camizestrant arm and 44.5% in the control arm), consistent with the known safety profile of CDK4/6 inhibitors. The frequency of discontinuation due to adverse events was 1.3% in the camizestrant arm and 1.9% in the control arm and the incidence of serious adverse events was 10.3% in camizestrant arm and 12.3% in the control arm.

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:

A clinical management algorithm is provided below.

Prior to being eligible for the proposed health technology, patients will have been diagnosed with HR-positive, HER2-negative mBC and have received at least 6 months of AI + CDK4/6 inhibitor and remain free of disease progression.

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?

No

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

NA

Use of the health technology

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

The key components and clinical steps involved in delivering a ctDNA extracted from blood plasma (liquid biopsy) genetic mutation test in patients with HR-positive/HER2-negative mBC are as follows:

- Oncologists who assess eligibility of patients for *ESR1*m testing and refer to a pathology collector or nurse to draw a blood sample from the patient. Samples are then sent to a NATA accredited clinical laboratory.
- A registered molecular pathologist and a registered anatomical pathologist are responsible for conducting the detection, diagnosis and reporting of the pathology result in a NATA accredited laboratory using NGS or dPCR to help guide and determine treatment.

- Special training (education and awareness) from the pathology laboratories maybe required at collection centres to ensure that blood samples are collected and transported in special tubes that are suitable sample stability and for subsequent ctDNA testing.

If the presence of *ESR1* activating mutations is confirmed, the patient may be eligible to receive PBS subsidised treatment with camizestrant.

A full cost effectiveness analysis will be presented in the integrated co-dependent submission including other healthcare resources used in conjunction with delivering the proposed testing.

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

As shown in the current treatment algorithm below, patients would receive no *ESR1*m testing and receive CDK4/6 inhibitor + AI, via the PBS.

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

Currently, there are no PBS-funded treatments available that specifically target patients with *ESR1* activating mutation tumours and as such, no testing for this mutation occurs as part of routine clinical practice.

With the availability of *ESR1*m testing, patients with confirmed *ESR1* activating mutations may be eligible for PBS-subsidised treatment with camizestrant.

Using *ESR1*m as a predictive biomarker for the benefit of camizestrant optimises treatment outcomes. This may create healthcare system efficiencies, in terms of costs and resource allocation.

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:

With the MBS listing of *ESR1*m testing, patients with confirmed *ESR1* activating mutations may be eligible to receive treatment with camizestrant (+ the CDK4/6 inhibitor the patient is already receiving).

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

Patients with newly diagnosed HR-positive, HER2-negative mBC will generally receive treatment with a CDK4/6 inhibitor + AI until disease progression or unacceptable toxicity (**Figure *1***). In a small proportion of patients (primarily patients with primary ET resistance or early relapse on/after adjuvant AI), fulvestrant is used in combination with a CDK4/6 inhibitor instead of an AI. Patients who have received adjuvant CDK4/6 inhibitor in the early BC setting are unable to be re-treated with a CDK4/6 inhibitor due to the current PBS once in a lifetime restriction and will therefore receive ET or chemotherapy, depending on their disease characteristics.

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

As shown in the proposed treatment algorithm below (Figure 2), the key difference between the current algorithm and the proposed algorithm, is that patients who have been treated with 1L CDK4/6 inhibitor + AI for at least 6 months, become eligible to be tested for *ESR1*m up to 6 times per year, at the same time as other routine testing. After a patient has tested positive for *ESR1*m, they may be eligible to receive PBS subsidised camizestrant in combination with the same CDK4/6 inhibitor they were receiving at the time of the testing. This change results in an increase in *ESR1*m testing and a decrease in AI utilisation in patients who test positive for *ESR1*m.

As per the study design of SERENA-6, some patients will require more than one *ESR1* mutation test, as *ESR1* mutations develop over time i.e. the requested MBS listing is for serial testing in patients who have HR-positive, HER2-negative mBC and have received at least 6 months of first line treatment with a CDK4/6 inhibitor + AI and who have not progressed radiographically or clinically.

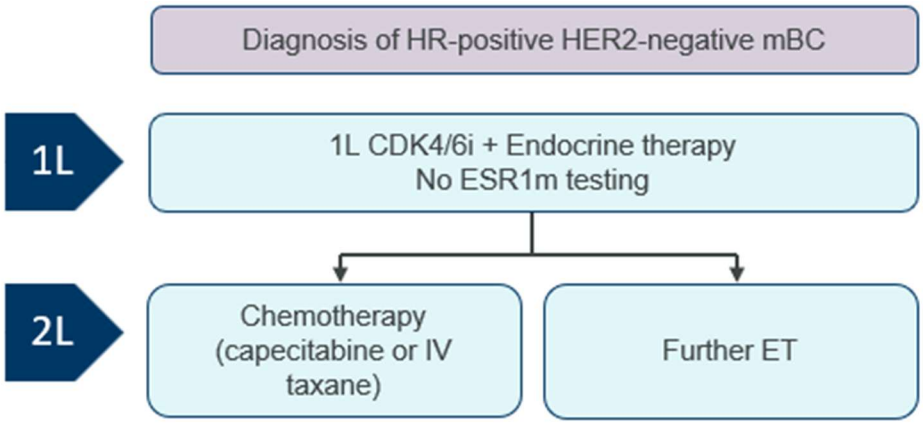
Algorithms

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

Note: Please ensure that the diagrams provided do not contain information under copyright.

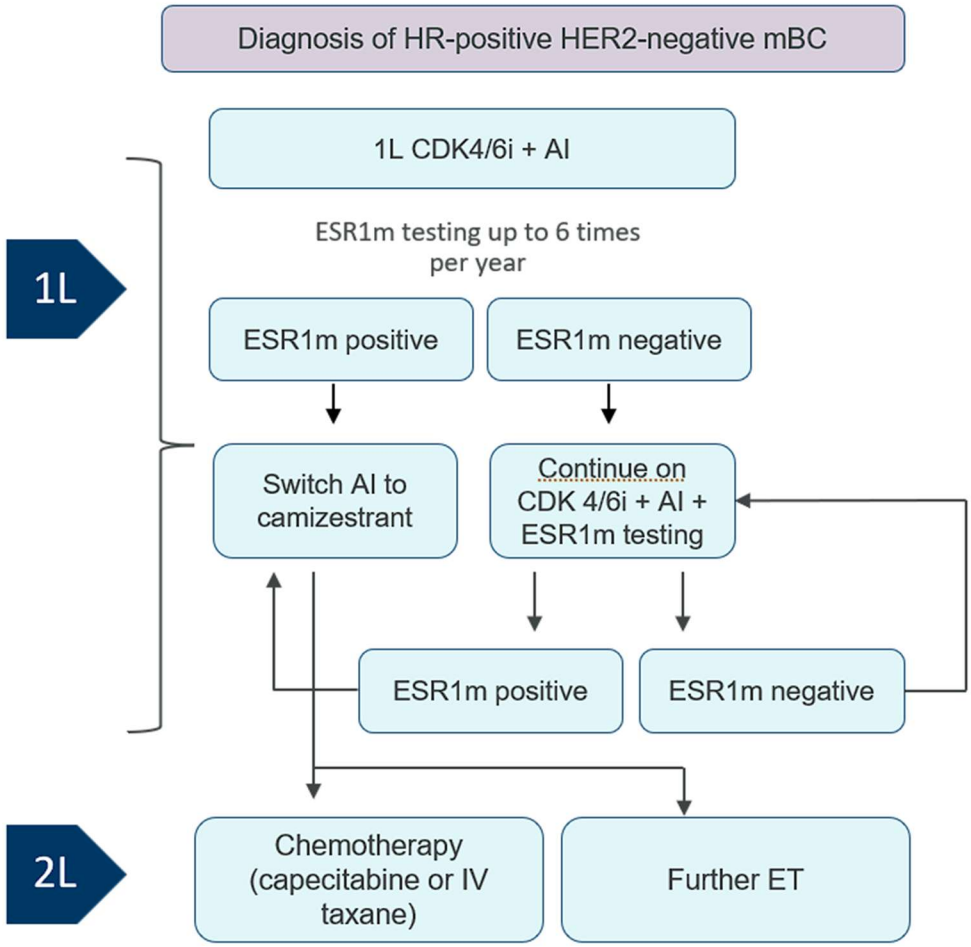
The current and proposed treatment algorithms are provided below in Figure 1 and Figure 2, respectively. The key change between the two algorithms is the addition of serial *ESR1*m testing by ctDNA commencing after at least 6 months of treatment with a CDK4/6 inhibitor (CDK4/6i) in combination with an AI. If the test result is ESR1m-positive, and there is no evidence of disease progression, camizestrant can be substituted in place of the AI. If the test result is ESR1m negative, the patient continues to receive the current therapy regimen and will be re-tested up to 6 times per year, if there is no evidence of disease progression.

Figure 1 Current Clinical Management Algorithm



Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; ET: endocrine therapy; IV: intravenous

Figure 2 Proposed Clinical Management Algorithm



Abbreviations: CDK4/6i: cyclin dependent kinase 4/6 inhibitor; ET: endocrine therapy; IV: intravenous

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)?

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Superiority versus no testing + standard of care

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
This application requests public funding for *ESR1*m testing as a diagnostic service to determine eligibility for camizestrant in combination with a CDK4/6 inhibitor for patients who have HR-positive, HER2-negative mBC who have received at least 6 months of first line treatment with a

CDK4/6 inhibitor in combination with an AI and whose disease has not progressed radiographically.

As described above, the results from the SERENA-6 trial demonstrate that switching from AI to camizestrant upon testing positive for *ESR1*m, results in an extension of time spent free of disease progression, with improved quality of life outcomes versus no testing and maintaining standard of care therapy.

Identify how the proposed technology achieves the intended patient outcomes:
*ESR1*m testing identifies the patients who are eligible to receive camizestrant.

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?	Yes

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?

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

The PBS listing of camizestrant will impact the utilisation of *ESR1*m testing by ctDNA liquid biopsy. A detailed utilisation analysis will be presented in the integrated co-dependent submission.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary (repeat columns as required).

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 (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
1	Phase 3 RCT	First line Camizestrant for Emerging *ESR1*-mutated Advanced Breast Cancer	Double-blind controlled study using ctDNA-testing to detect emergent *ESR1* mutations during 1L AI+CDK4/6 therapy in HR+/HER2– mBC. Switching to camizestrant while continuing the same CDK4/6 inhibitor significantly prolonged mPFS and delayed quality-of-life deterioration versus continuing AI, with manageable safety *This publication is from DCO1. Data from DCO2 anticipated to be available for the integrated co-dependent submission.*	https://www.nejm.org/doi/full/10.1056/NEJMoa2502929	2025
2	Phase 3 RCT	Patient-reported outcomes in the SERENA-6 trial of camizestrant plus CDK4/6 inhibitor in patients with advanced breast cancer and emergent *ESR1* mutations during 1st-line endocrine-based therapy	This publication reports on Patient Reported Outcomes from the phase 3 SERENA-6 trial (ref 1). Switching to camizestrant-CDK4/6i delayed time to deterioration and reduced risk of deterioration in cancer symptoms (pain HR 0.57; fatigue HR 0.75; dyspnoea HR 0.52), breast (HR 0.74) and arm symptoms (HR 0.69) & functioning (physical HR0.74; role HR 0.73; emotional HR 0.51) versus continuing on AI+CDK4/6i. Tolerability was high.	https://doi.org/10.1016/ j.annonc.2025.10.006	2025
3	Phase 3 RCT	Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising *ESR1* mutation during AI + palbociclib therapy (PADA-1): a randomised, open-label, multi-centre, phase 3 trial	The PADA-1 trial was the first prospective RCT showing that the early therapeutic targeting of ESR1 mutations detected in blood results in significant clinical benefit. At rising *ESR1*m without progression, HR+ patients were randomised to switch AI to fulvestrant (continue palbociclib) or continue AI+palbociclib. Switching improved median PFS (11.9 vs 5.7 months; HR 0.61) with similar safety.	https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00555-1/fulltext	2022

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
4	Review	ESR1 mutations as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer	ESR1-MUT arises in patients who receive AI in the metastatic setting, and this causes resistance to AI monotherapy, with cfDNA detection of ESR1-MUT preceding radiologic progression by 3-7 months	https://doi.org/10.1186/s13058-021-01462-3	2021
5	Real-world data study	Real-world clinical-genomic data identifies the ESR1 clonal and subclonal circulating tumor DNA (ctDNA) landscape and provides insight into clinical outcomes	Uniquely well-characterized clinical-genomic data in a proprietary dataset identified that approx. 30% of patients with advanced breast cancer had somatic *ESR1* mutations following AI therapy, consistent with previously published data. The majority of patients had multiple subclonal ESR1 resistance mutations following AI treatment.	https://doi.org/10.1158/1538-7445.SABCS20-PS18-15	2021
6	Prospective observational cohort study	Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer	In a prospective cohort of HR+/HER2- mBC patients treated with AIs, serial ctDNA testing showed ESR1 mutations in 56% at progression, detectable a median 6.7 months before clinical progression and often polyclonal/subclonal. Findings highlight substantial genomic heterogeneity and early, ctDNA-detectable resistance, informing pre-progression treatment adaptation strategies.	https://www.sciencedirect.com/science/article/pii/S0923753419349774	2018

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
7	Phase 3 RCT	Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial	Randomised, open-label study in ER-positive/HER2-negative advanced breast cancer post-CDK4/6 inhibitors. Elacestrant 400 mg daily improved progression-free survival versus standard endocrine therapy overall (HR 0.70), with a more pronounced benefit in *ESR1*-mutant disease (HR 0.55). PFS improvement in the ITT population was largely driven by *ESR1*-mutant results. Safety was manageable.	https://ascopubs.org/doi/pdf/10.1200/JCO.22.00338	2022
8	Phase 3 RCT	Imlunestrant with or without Abemaciclib in Advanced Breast Cancer	Randomised, open-label study in ER-positive/HER2-negative advanced breast cancer after aromatase inhibitor ± CDK4/6. Imlunestrant (oral SERD) improved PFS versus standard therapy in *ESR1*-mutant patients (median 5.5 vs 3.8 months). PFS in the overall population was not significant (HR 0.87). Imlunestrant–abemaciclib significantly improved PFS versus imlunestrant, regardless of *ESR1*-mutation status	https://www.nejm.org/doi/pdf/10.1056/NEJMoa2410858	2025
9	Phase 3 RCT	Vepdegestrant, a PROTAC Estrogen Receptor Degrader, in Advanced Breast Cancer	Randomised, open-label study comparing vepdegestrant (PROTAC ER degrader) versus fulvestrant in ER-positive/HER2-negative advanced breast cancer after prior CDK4/6. Blinded central review showed higher ORR and clinical benefit with vepdegestrant, especially in *ESR1*-mutant disease (ORR 18.6% vs 4.0; CBR 42.1% vs 20.2%). PFS benefit concentrated in *ESR1*-mutants, not overall. Safety was manageable.	https://www.nejm.org/doi/pdf/10.1056/NEJMoa2505725	2025