Medical Services Advisory Committee (MSAC)
Public Summary Document

Application No. 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

Applicant: **AstraZeneca Pty Ltd.**

Date of MSAC consideration: **29 November 2024**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1.   Purpose of the application

The integrated codependent application was received from AstraZeneca Pty Ltd by the Department of Health and Aged Care in June 2024, which requested:

- Medicare Benefits Schedule (MBS) listing of Next Generation Sequencing (NGS) testing of tumour tissue for the evaluation of AKT pathway alterations (*PIK3CA/AKT1/PTEN*[1]) to determine eligibility for treatment with capivasertib in combination with fulvestrant (CAPI+FULV) in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) locally advanced (unresectable) or metastatic breast cancer following disease progression or recurrence on or after an endocrine-based regimen with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.

- Pharmaceutical Benefits Scheme (PBS) General Schedule Authority Required (Telephone/Online) listing of capivasertib with fulvestrant for the treatment of HR+/HER2- locally advanced (unresectable) or metastatic breast cancer following disease progression or recurrence on or after an endocrine-based regimen with or without a CDK4/6 inhibitor in patients who have evidence of an AKT pathway alteration (*PIK3CA, AKT1,* or *PTEN*).

The key PICO components presented in the submission are presented in Table 1.

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[1] PIK3CA = Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; AKT1 = serine/threonine kinase; PTEN = phosphatase and tensin homolog

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Patient with newly diagnosed locally advanced or progression to metastatic HR+ /HER2- breast cancer Drug: Patients with AKT pathway altered (*PIK3CA*, *AKT1* or *PTEN*) tumours will be eligible for CAPI+FULV treatment in 1L or 2L metastatic setting.
Intervention	Test: A test of tumour tissue for the detection of an AKT pathway altered (*PIK3CA*, *AKT1* or *PTEN*) tumour. Drug: CAPI 400 mg (two 200 mg tablets) administered orally twice daily, for 4 days on-treatment followed by 3 days off-treatment in combination with FULV 500 mg (2 x 250mg/5 ml) intramuscular injections at intervals of 1 month. An additional 500 mg dose is to be given 2 weeks after the initial dose
Comparator	Test: No testing Drug: FULV monotherapy
Outcomes	PFS, OS, PFS2, QoL, safety and tolerability
Clinical claim	In patients with AI-resistant HR+/HER2- locally advanced or metastatic breast patients with confirmed AKT pathway altered (*PIK3CA*, *AKT1*, or *PTEN*) tumours, the addition of CAPI+FULV vs. FULV monotherapy led to statistically significant superior PFS outcome and inferior but manageable safety outcome.

Source: Table 1.1, p9 of the submission
AI = aromatase inhibitor; AKT = serine/threonine protein kinase; CAPI = capivasertib; FULV = fulvestrant; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomisation to second progression or death; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; PTEN = phosphatase and tensin homolog; QoL = quality of life; 1L = first line setting; 2L = second line setting.

Alignment with agreed PICO confirmation

The submission did not align with the PASC-ratified PICO Confirmation (April 2024 PASC) as shown in Table 2.

Table 2 Compliance with the Ratified PICO Confirmation (April 2024 PASC meeting)

PICO Component	Compliance	Change and justification provided in submission
Proposed MBS listing	No	The submission's MBS item descriptor was broader than the PICO confirmation and is discussed in detail in Section 6. The submission did not justify this change.
Population / clinical indication (test population)	No	The submission's PICO test population were "patients with newly diagnosed locally advanced or progression to metastatic HR+/HER2- breast cancer" and was broader than the PICO confirmation which included "patients with locally advanced (inoperable) or metastatic HR+/HER2– or HER2-low breast cancer following recurrence or progression on or after AI therapy, with or without a CDK4/6 inhibitor". The submission did not justify this change.
Population / clinical indication (treatment population)	No	The submission's PICO treatment population stated, "patients with AKT pathway altered (*PIK3CA, AKT1 or PTEN*) tumours will be eligible for capivasertib + fulvestrant treatment in 1L or 2L metastatic setting" and was broader than the PICO confirmation which included "patients in the test population with a tier 1 genetic variant in the AKT pathway, for second line treatment". The submission did not justify this change.
Intervention (test)	No	The submission's PICO test was "a test of tumour tissue for the detection of an AKT pathway altered (*PIK3CA, AKT1 or PTEN*) tumour" and this definition was less granular than the PICO confirmation which stated "tumour tissue testing using NGS to characterise tier 1 genetic variants in all three genes (*PIK3CA, AKT1 and PTEN* genes) associated with abrogation of the AKT pathway". The submission did not justify this change.
Comparator	No	The submission nominated FULV monotherapy as the main comparator. The PASC stated the comparator to be "SOC which included a range of different treatment options and no clear standard of care for second line treatment (alternative ET + CDK4/6 inhibitor, EVE+EXE/FULV/tamoxifen, chemotherapy)". See Section 8.
Reference/evidentiary standard	Yes	Consistent with the PICO confirmation.
Clinical management algorithm	Yes	The submission's clinical algorithm was mostly consistent with the PICO confirmation, except the PICO confirmation also considered treatments after the 2L setting and the submission did not. The submission did not justify this change.
Clinical outcomes assessed	Yes	Consistent with the PICO confirmation.

Source: Table 1.1, p9; Table 1.5, p21; and Figure 1.4, p17 of the submission; Table 1, pp2-4; p26; and Figure 5, p22 of the 1766 Ratified PICO Confirmation, April 2024 PASC Meeting
AI = aromatase inhibitor; AKT = serine/threonine protein kinase; CDK4/6 = cyclin dependent kinase 4 and 6; ET = endocrine therapy; EVE = everolimus; EXE = exemestane; FULV = fulvestrant; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; NA=not applicable; NGS = Next Generation Sequencing; PASC = PICO Confirmation Advisory Sub-Committee; PICO = population, intervention, comparator, outcome; SOC = standard of care; 1L = first line setting; 2L = second line setting.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of next generation sequencing genetic testing to detect AKT pathway alterations in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) locally advanced or metastatic breast cancer, to determine eligibility for Pharmaceutical Benefits Scheme (PBS) subsidised capivasertib treatment.

MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend capivasertib for treatment of HR+ HER2- locally advanced or metastatic breast cancer with

evidence of AKT pathway alteration, following recurrence or progression on or after endocrine therapy in its November 2024 meeting.

MSAC considered that the claim of codependence between testing for AKT pathway alterations and treatment benefit with capivasertib was not strong as patients appeared to have some progression-free survival benefit from capivasertib irrespective of whether their tumours had an AKT pathway alteration. MSAC considered that it might be inequitable to exclude these patients from access to treatment based on the current evidence. MSAC advised that further evidence would be required to confirm if AKT pathway alteration is a treatment effect modifier, and therefore to better support the clinical claim of codependence.

Consumer summary

This is a co-dependent application from AstraZeneca Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of testing for AKT pathway alterations in people with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) locally advanced (unresectable) or metastatic breast cancer so that they can access the medication, capivasertib, on the Pharmaceutical Benefits Scheme (PBS).

Some people with breast cancer might have alterations in the genetic code of their cancer cells that can make the cancer more active. One type of genetic alteration is called "AKT pathway alteration". AKT is a protein that promotes cell growth and survival. People with "AKT pathway alterations" in their cancer cells may have increased activity of the AKT protein, which may lead to overactive cancer cells. The alterations can be detected by genetic testing of 3 genes: *PIK3CA*, *AKT1* and *PTEN*. Capivasertib is a medication that blocks the activity of the AKT protein, and is thought to help patients with breast cancer who have alterations in their AKT pathway genes. In this application, capivasertib is proposed to be used with another drug called fulvestrant.

HR+/HER2- advanced breast cancer affects about 17,000 people in Australia each year. Outcomes for these patients are often poor, so there is a need for better treatments for this group of patients.

MSAC considered the genetic testing to be safe. However, MSAC was concerned that there was not enough evidence to show that people with an AKT pathway alteration will benefit more from capivasertib than people who don't have the AKT pathway alteration. MSAC considered that there was some evidence to support the claim that patients with AKT pathway alterations had better progression-free survival when they were treated with capivasertib+fulvestrant treatment, compared to when they were treated with fulvestrant alone. However, it also appeared that some patients who did not have AKT pathway alterations had better progression-free survival after capivasertib+fulvestrant treatment. This meant that MSAC was not certain if it was reasonable to limit capivasertib+fulvestrant treatment to only patients with AKT pathway alterations; it would be inequitable to limit access to capivasertib if it could benefit a wider population.

The Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend listing capivasertib on the PBS. Because PBAC's decision meant that the test could not be used to access capivasertib on the PBS, MSAC did not support listing testing for AKT pathway alterations on the MBS. MSAC also considered that more evidence of the connection between AKT pathway testing and capivasertib effectiveness was needed, as well as a price justification for the test, which was more expensive than other similar tests on the MBS.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support listing AKT pathway testing on the MBS for patients with HR+/HER2- locally advanced or metastatic breast cancer. The claim that people with an AKT pathway alteration will benefit more from capivasertib than people without the AKT alternation was not proven, and the cost of testing was high without justification. Also, the PBAC did not recommend listing capivasertib on the PBS, and with no drug to access on the PBS, MSAC considered that there is no need for AKT pathway testing at present.

3.   Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a co-dependent application from AstraZeneca Pty Ltd requesting:

1.1   MBS listing of NGS testing of tumour tissue for AKT pathway alterations in the *PIK3CA*, *AKT1* and *PTEN* genes in patients newly diagnosed with locally advanced (unresectable) or metastatic HR+, HER2- breast cancer.

1.2   PBS listing of capivasertib (CAPI) with fulvestrant (FULV, i.e., CAPI+FULV) for the targeted treatment of patients with locally advanced (unresectable) or metastatic HR+, HER2– breast cancer following disease progression or recurrence on or after an endocrine-based regimen with or without a CDK4/6 inhibitor and with evidence of AKT pathway alterations.

MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend CAPI at its November 2024 meeting due to a high incremental cost-effectiveness ratio (ICER), low clinical benefit with inappropriate choice of comparator, and significant toxicity. The PBAC advised that any resubmission would need to undergo the standard re-entry pathway.

MSAC noted that there are over 20,000 cases of breast cancer per year in Australia and that approximately 70% of these cases are estimated to be HR+/HER2–. MSAC noted that AKT pathway alterations are common in advanced breast cancer and can be as high as 60% of patients with HR+/HER2– breast cancer, although the Australian rates are unknown. *PIK3CA* is the most common gene alteration, followed by *AKT1* and then *PTEN*. These genetic variants can be present at the time of cancer recurrence, or may be acquired as a result of previous treatment. CAPI is an AKT inhibitor and TGA-approved in combination with FULV for the treatment of adult patients with HR+/HER2- locally advanced or metastatic breast cancer following recurrence or progression on or after an endocrine-based regimen.

MSAC noted that treatment resistance and death are highly likely in patients with locally advanced or metastatic HR+/HER2– breast cancer, and therefore that new, effective treatments for this patient group are needed.

MSAC noted the proposed MBS descriptor, which was:

'A test of tumour tissue for full characterisation of tier 1 *PIK3CA*, *AKT1* and *PTEN* gene variants including *PTEN* copy number variants, associated with abrogation of the AKT pathway, in a patient with:
- locally advanced (inoperable) or metastatic hormone receptor positive, HER2- breast cancer; OR
- following recurrence or progression on or after endocrine based regimen, with or without a CDK4/6 inhibitor.

As requested by a specialist or consultant physician, to determine eligibility for a relevant treatment listed on the Pharmaceutical Benefits Scheme (PBS) for this context.'

MSAC considered that the use of 'OR' within the descriptor resulted in a lack of alignment between the proposed testing item and the proposed PBS restriction. MSAC noted that 'OR' might be reasonable clinically as a means of saving time (because it allows for testing at the first occurrence of cancer, resulting in treatment being initiated sooner after recurrence or progression). However, MSAC also considered that testing prior to breast cancer recurrence or progression may also lead to missing AKT pathway alterations that may develop later. MSAC further noted that the number of patients tested per year would depend on whether the item descriptor restricted testing to patients after cancer recurrence or progression (i.e. if the descriptor used 'AND' as opposed to 'OR'), or permitted testing on initial diagnosis (as proposed). MSAC considered that 'AND' was a better word choice because it would limit the testing population to second-line use only, as proposed in the PBS restriction and the ratified PICO Confirmation.

MSAC noted that the department sought advice on whether the item descriptor should be amended to refer to fresh tumour tissue. While MSAC noted that testing would have lower failure rates if

performed on fresh biopsy tissue (rather than formalin-fixed tissue), MSAC considered that the requirement for fresh tumour tissue would present significant practical barriers to accessing this item as formalin fixed tissue is normally used for tumour testing, and that the pivotal trial data did not specify a requirement for fresh tumour tissue. MSAC acknowledged that opportunities for re-biopsy are often very limited. Thus, MSAC advised that the MBS item descriptor should refer to 'tumour tissue', without requiring tissue to be freshly acquired.

MSAC noted that the removal of the restriction to tier 1 variants in the proposed item descriptor was consistent with previous advice from the ESCs. MSAC noted that it is unnecessary for MBS item descriptors to specify the test result required to grant PBS access, and it is sufficient to only specify the genes being tested (i.e. AKT pathway testing). MSAC considered the removal of the tier 1 variant wording was reasonable as an equivalent restriction to pathogenic or likely pathogenic variants is already required by the PBS listing. MSAC further noted that removal of this wording was in alignment with other similar MBS items, such as item 73437, which allows for NGS testing for non-small cell lung cancer (NSCLC).

MSAC also recommended removal of the words 'associated with abrogation of the AKT pathway' in the item descriptor, as MSAC considered this to be not clinically necessary.

MSAC noted that the proposed item fee ($2,200) was significantly higher than the fees for other similar MBS items, for example, MBS item 73437 ($1,247). MSAC considered that the proposed fee was reasonable only if comprehensive genomic profiling (CGP) testing was performed and required. However, MSAC considered that the need for CGP testing was not clearly justified, as the testing would be performed for 3 genes only and more targeted options for testing were available, which could reduce both costs and failure rates. MSAC advised that a re-application should provide further information around the need for CGP or, alternatively, propose a more targeted testing option and revise the proposed fee.

MSAC noted that the proposed item descriptor states that the testing is 'As requested by a specialist or consultant physician', but that the department proposed this be updated to include the wording '...by, or on behalf of, a specialist or consultant physician'. MSAC considered it appropriate to include 'on behalf of' to expedite testing, and considered that pathologists should also be able to request the item on behalf of a specialist or consultant physician.

MSAC considered that the restriction of testing to once per primary tumour diagnosis was reasonable, and takes into account scenarios where a patient may get a second, primary breast cancer in either breast. MSAC noted that in the event of test failure and subsequent re-testing, patients would not typically incur out of pocket costs, because a valid result must be reported before a pathology item can be billed. In instances where insufficient sample is provided and a recollection is necessary, the pathology provider is expected to absorb the cost. Thus, MSAC considered that overall, it was reasonable to retain the restriction even after taking into account failure rates.

MSAC noted that although there were no major issues with how the testing was depicted in the clinical management algorithm, comparator treatment options were broader than FULV only, and in many cases these alternative treatments would likely be more effective than FULV alone.

MSAC noted the clinical claim that CAPI+FULV was superior to placebo+FULV in patients with AKT pathway alterations (using progression-free survival [PFS] as the health outcome), and that it had inferior but manageable safety. MSAC noted that, although re-biopsy for testing at disease recurrence or progression, is associated with some additional risks, the need for re-biopsy is unlikely. Since there were no other risks from the testing (aside from flow-on effects due to false positive and negative results), MSAC considered that there were no significant safety issues associated with AKT testing. MSAC considered that the primary safety issues were associated with treatment rather than testing, noting the PBAC's concerns about the toxicity of CAPI treatment.

MSAC noted ESC's concerns about the limited evidence demonstrating concordance between different testing methods (i.e. FoundationOneCDx, used in the pivotal CAPItello-291 trial, vs Roche

AVENIO CGP, proposed by the applicant for use in Australia). These issues included the very small sample sizes used to verify concordance and the uncertainty about which test kit would be adopted in Australia. MSAC noted a recent abstract which evaluated the performance of the proposed Roche Avenio CGP kit across multiple laboratory settings.[2] In the pre-MSAC response, the applicant argued that the limited standardisation of testing modalities across laboratories was due to the current lack of MBS reimbursement for the testing. The applicant stated that the Roche AVENIO CGP kit and similar tests will be used in NATA-accredited laboratories and their use would be monitored by the Royal College of Pathologists of Australasia via a Quality Assurance Program.

The main clinical trial demonstrating prognostic and predictive validity of the test was CAPItello-291, which compared overall survival (OS) and PFS for AKT pathway-altered and non-AKT pathway-altered populations, treated with the intervention or comparator. MSAC noted the joint ESCs' concerns about the clinical effectiveness of CAPI+FULV, which considered the OS data to be immature and the comparator (FULV alone) to be questionable.

For AKT pathway-altered populations, MSAC noted that PFS appeared to improve with CAPI+FULV treatment (hazard ratio [HR] 0.50, 95% CI 0.38, 0.65). MSAC considered that the PFS benefit observed in the AKT pathway altered groups relative to the known non-AKT pathway altered group was equivocal, as the analysis was conducted *post hoc*, was not adjusted for multiplicity, and characteristics for these subgroups were not presented in the submission. However, MSAC noted that the pre-MSAC response provided additional information demonstrating that baseline characteristics were balanced across the subgroups in both treatment arms to support the robustness of the *post hoc* analysis. MSAC also noted that there was a trend towards PFS benefit in the known non-AKT pathway altered group (HR 0.79, 95% CI 0.61, 1.02), but considered that this could be due to unidentified alterations (resulting from either test failure or alterations that were acquired after testing).

For OS, there was a trend towards statistical significance in the AKT pathway altered population (HR 0.69, 95% CI 0.46, 1.05), however there was no statistically significant difference found between the treatment arms, which was likely due to the OS data being immature. No OS benefit in the known non-AKT pathway altered population was found.

Overall, MSAC considered the co-dependency claim is likely to be reasonable but needed further justification, because the trial results suggested that patients appeared to have some PFS benefit from CAPI irrespective of whether their tumours had a AKT pathway alteration, and because the key evidence demonstrating a PFS benefit was based on *post hoc* analyses. MSAC considered that based on the current evidence, it might be inequitable to exclude non-AKT pathway altered patients from access to treatment. MSAC advised that further evidence would be required to confirm if AKT pathway alteration is a treatment effect modifier, and therefore to better support the clinical claim of codependence.

MSAC noted that the economic evaluation was a cost-utility analysis that assumed 99% specificity, 99% sensitivity, 5% failure rate and **redacted**% uptake. MSAC noted that the failure rate reported in the CAPItello-291 trial was 15%, and therefore the 5% failure rate used in the analysis was not well justified. MSAC noted the applicant's claim that failure rates would be lower with improvement in biopsy sample collection and education in the Australian setting, but MSAC did not consider that this was likely to be the case. MSAC noted that the economic model applied a testing cost of $**redacted** per patient. However, the failure rate and cost of the test did not have a significant impact on the ICER.

MSAC noted that the ICER was $75,000 to <$95,000 per quality-adjusted life year (QALY) gained. If CAPI was available without AKT pathway testing (that is, was available to all patients regardless

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[2] Choi J, Fellowes A, Pikarsky E et al. 2023. 'Performance assessment of a comprehensive genomic profiling (CGP) NGS kit across multiple study laboratories', Annals of Oncology 34, Supplement 2S263.

of AKT pathway status), the ICER would increase to $95,000 to <$115,000/QALY gained. Key drivers of the ICER were the cost of CAPI, and the modelled OS in both the CAPI+FULV group and the placebo+FULV group, noting that the difference in OS between these two groups was not statistically significant in the CAPItello-291 trial.

MSAC noted the financial impact to the MBS (including 88% of patients who progress from first-line to second-line therapy) was $0 to <$10 million in year 1, increasing to $0 to <$10 million in year 6 (Table 18). MSAC considered these estimates to be reasonable, with the first-year financial impact possibly underestimated.

MSAC considered that major implementation issues are unlikely as NGS testing is established in other cancers. However, there might be equity issues relating to the timeliness of testing and access to biopsies in rural and regional areas.

Overall, MSAC did not support public funding of testing for AKT pathway alterations in patients with HR+/HER2- locally advanced or metastatic breast cancer. MSAC considered that there was no clinical indication for AKT pathway testing, as PBAC did not recommend the proposed PBS-listing of CAPI. MSAC advised that a resubmission should address the issues regarding the claim of co-dependency, greater details about potential rate of missed alterations in 'known non-AKT pathway altered' group, justification of the need for CGP (and therefore the cost of the testing), and revised economics around failure rates. MSAC considered the resubmission should be considered by ESC.

4.   Background

While this is the first submission of CAPI, there are two other MSAC applications of potential interest, which are presented in Table 3.

Table 3: MSAC applications of interest

	MSAC 1604 [3]	MSAC 1783 [4]
Application process	Completed the PICO process in February 2020 (1604 Ratified PICO Confirmation), though status of submission for PBS-listing was not known	Considered by PASC in August 2024 (ratified PICO confirmation pending) and is yet to be considered by MSAC
Population	Patients with HR+/HER2- advanced breast cancer, who have progressed on or after treatment with an AI or CDK4/6 inhibitor	Patients with HR+/HER2- locally advanced or metastatic breast cancer
Biomarker	*PIK3CA*	*PIK3CA*
Test	Tissue or plasma sample testing. The exact assay and relevant costs were not specified.	Tissue or plasma sample testing using a NGS assay. The exact assay was not specified. Indicative cost of $350-$400 per test.
Intervention	Alpelisib + FULV	Inavolisib
Comparator test	No testing	No testing
Comparator treatment	Standard care 1L setting: CDK4/6 inhibitor + NSAI or ribociclib + FULV 2L setting: EVE+EXE or ribociclib + FULV	Palbociclib + FULV

Source: 1604 Ratified PICO Confirmation; MSAC Application 1783 PICO set document
AI = aromatase inhibitor; AKT = serine/threonine protein kinase; CDK4/6 = cyclin dependent kinase 4 and 6; EVE = everolimus; EXE = exemestane; FULV = fulvestrant; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; NGS = Next Generation Sequencing; NSAI = non-steroidal aromatase inhibitor; PASC=PICO Confirmation Advisory Sub-Committee; PBS = Pharmaceutical Benefits Scheme; PICO = population, intervention, comparator, outcome; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; 1L = first line setting; 2L = second line setting

5. Prerequisites to implementation of any funding advice

The submission proposed that the Roche AVENIO Comprehensive Genomic Profiling (CGP) assay would be the test used in Australia for the detection of *PIK3CA, AKT1*, or *PTEN* alterations in patients with HR+/HER2- locally advanced (unresectable) or metastatic breast cancer. Roche AVENIO CGP is an in-house Next Generation Sequencing (NGS) pan-cancer assay that provides comprehensive genomic profiling of solid tumours from formalin-fixed paraffin-embedded (FFPE) tissue samples, including *PIK3CA, AKT1,* and *PTEN* pathway alterations.

Roche AVENIO CGP is not currently TGA-approved, and it was not apparent in the submission if there was intent to register this test on the Australian Register of Therapeutic Goods (ARTG). The submission stated that NGS that is not approved by the TGA as a commercial test, is considered to be an in-house in vitro diagnostic (IVD) device, and is subject to regulation according to the IVD regulatory framework. The submission stated there are 27 National Association of Testing Authorities (NATA) accredited organisations that provide DNA sequencing of human tissue using NGS technology in Australia. The submission stated that the laboratory conducting the NGS genetic testing would be monitored and audited by the Royal College of Pathologists of Australasia (RCPA) via a Quality Assurance Program.

The commentary considered that since Roche AVENIO CGP is not TGA-approved (and intention for registration was not apparent), it was not clear which test would actually be used in clinical practice. The submission noted that there are two NGS IVD devices approved by the ARTG: the Illumina (ARTG ID 297844) and the ThermoFisher Scientific OncomineDx (ARTG ID 426895). However, it was not known if the Illumina or ThermoFisher NGS tests would also be used in clinical practice to identify AKT pathway altered patients. In addition, the submission noted that other in-house NGS assays could be used by laboratories for AKT pathway testing; however, these assays

[3] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1604-public
[4] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1783-public

were not specified. As such, the commentary considered there was uncertainty as to whether accredited pathology services would adopt the Roche AVENIO CGP as the in-house assay or whether an independently developed in-house assay would be used for AKT pathway testing.

The submission proposed that a specialist clinician (e.g., medical oncologist, breast surgeon, interventional radiologist) will request AKT pathway alteration testing. Fresh tumour tissue samples are preferred for AKT pathway testing. The commentary noted this was also noted by PASC (p11, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting) and consistent with the pivotal trial, CAPItello-291. However, there may be downstream consequences of re-biopsy in terms of safety and costs given the preference for fresh tumour tissue (see Section 11). The patient's tumour tissue sample would be sent to a NATA-accredited pathology laboratory to conduct NGS genetic testing, where a registered molecular/anatomical pathologist is responsible for conducting the detection, diagnosis and reporting of the pathology result. Based on a positive AKT pathway alteration (*PIK3CA*, *AKT1* or *PTEN*) test result, the medical practitioner will consider prescribing CAPI+FULV to the patient if they meet the PBS criteria to access treatment.

6. Proposal for public funding

The submission's proposed MBS item descriptor is presented in Table 4.

Table 4: Proposed new MBS item in the submission

Category 6 – PATHOLOGY SERVICES
MBS item XXXX A test of tumour tissue for full characterisation of tier 1 *PIK3CA, AKT1* and *PTEN* gene variants including *PTEN* copy number variants, associated with abrogation of the AKT pathway, in a patient with: •   locally advanced (inoperable) or metastatic hormone receptor positive, HER2- breast cancer; OR •   following recurrence or progression on or after endocrine based regimen, with or without a CDK4/6 inhibitor. As requested by a specialist or consultant physician, to determine eligibility for a treatment listed on the Pharmaceutical Benefits Scheme (PBS) for this context. Once per primary tumour diagnosis
Fee: $2,200   Benefit: 75% = $1,650   85% = $1,870

Source: Table 1.5, p21 of the submission
The commentary noted the submission applied the 85% Medicare rebate and did not consider the Greatest Permissible Gap of $98.70. The MBS fee after applying the Greatest Permissible Gap was $2,101.30.

The commentary noted that the submission's proposed MBS item descriptor was broader than the testing population in the ratified PICO confirmation (p25, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting):

> "A test of tumour tissue for full characterisation of tier 1 *PIK3CA, AKT1 and PTEN* gene variants including PTEN copy number variants, associated with abrogation of the AKT pathway, in a patient with:
> - locally advanced (inoperable) or metastatic hormone receptor positive, HER2- breast cancer; <u>AND</u>
> - following recurrence or progression on or after <u>aromatase inhibitor therapy</u>, with or without a CDK4/6 inhibitor.
>
> As requested by a specialist or consultant physician, to determine eligibility for a treatment listed on the Pharmaceutical Benefits Scheme (PBS) for this context.
> Once per primary tumour diagnosis."

The commentary noted that the PICO confirmation stated (p26, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting) that:

> "The applicant proposed MBS item descriptor was amended to include "AND following recurrence or progression on or after aromatase inhibitor therapy, with or without a CDK4/6 inhibitor", so as to be consistent with the target test population as well as the study population in the CAPitello-291 trial."

The commentary considered that the MBS item descriptor in the submission, which included 'OR' rather than 'AND', implied that some patients could be tested without progression from a prior endocrine therapy (ET) (i.e., patients with *de novo* advanced or metastatic breast cancer).

Additionally, the commentary considered progression on an 'endocrine-based regimen' was broader than progression on an 'aromatase inhibitory (AI) therapy' as noted in the PICO confirmation. Furthermore, the commentary considered the submission's MBS item descriptor was broader than the requested PBS restriction which only allows for treatment with CAPI+FULV following disease progression or recurrence on or after an ET with or without a CDK4/6 inhibitor.

The commentary noted that ETs are used in multiple lines of treatment for HR+/HER2- breast cancer, including early and advanced stages, thus the current wording of the MBS item descriptor also allows testing in patients who have progressed to the first-line (1L), second-line (2L), and third-line (3L) settings. The commentary considered there is a lack of clarity in the time at which patients are tested (and treated). Notably:

- In the 1766 Ratified PICO Confirmation, the PASC noted that AKT pathway testing is mainly for determining eligibility for 2L treatment with CAPI+FULV and considered CAPI+FULV against comparator therapies in the 2L setting.

- The National Comprehensive Cancer Network (NCCN) 2024 guidelines also recommend CAPI+FULV in the 2L setting.

- The pivotal trial CAPItello-291 mostly supported testing and treatment in the 2L setting as it included primarily patients who had one prior line of ET for the locally advanced or metastatic disease (76% [539/708]).

The submission's proposed cost for AKT pathway testing using the Roche AVENIO CGP was $2,200. The submission also presented the costs for the Illumina TSO500 ($2,000) and the FoundationOneCDx (USD$3,000), along with MBS fees from 'similar' tests:

- MBS item 73433 NGS test for *NTRK1, NTRK2, NTRK3* in tumour tissue, fee $1,000.

- MBS item 73337 test for *EGFR* gene in tumour tissue, fee $397.35.

- MBS item 73307, test for Homologous recombination deficiency status, fee $3,000.

- MBS item 73296 test for various germline gene variants, including *BRCA1/2* genes, fee $1,200.

The commentary noted that PASC noted that while there was no consensus on cost or market price, it was believed that testing cost will eventually reduce (p26, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting). The commentary also noted that the 1783 MSAC Application for inavolisib in *PIK3CA*-altered patients proposed a $400 fee for NGS testing for the detection of *PIK3CA* alterations and the indicative cost for NGS testing was $350 to $400. Note that MSAC application 1783 was considered by PASC in August 2024 and has yet to be considered by MSAC.

The commentary considered the submission's application of an 85% MBS benefit of $1,870 (i.e., $330 out-of-pocket cost to the patient) was not reasonable given the Greatest Permissible Gap (GPG) would apply such that the MBS benefit to the patient would be $2,101.30 (GPG of $98.70 as of 1 November 2023).

The commentary also noted the submission did not describe how patients whose tumour tissue sample fails testing would be managed in practice. Additionally, given AKT pathway alterations are a somatic mutation, some patients whose initial test result is non-positive may develop an AKT pathway alteration after disease progression. The commentary considered it unclear if these patients would be eligible for a subsequent test. The MBS item descriptor testing is only 'once per primary tumour diagnosis', and the commentary considered this may present an equity issue for patients who pay out-of-pocket for subsequent testing.

7.   Population

In 2023, it was estimated that 20,672 new cases of breast cancer were diagnosed in Australia,[5] approximately 70% of which were likely to be HR+/HER2-. HR+ breast cancer is characterised by cancer cells that have receptors for oestrogen and/or progesterone.[6]

The biomarkers addressed in this submission are the *PIK3CA, AKT1,* and *PTEN* gene variants on the AKT signalling pathway. AKT pathway alterations (*PIK3CA, AKT1,* or *PTEN*) are somatic variants that are common in patients with the HR+/HER2- subtype. The submission noted that up to 50% of patients may have an alteration, mainly caused by alterations in *PIK3CA* (~35%) followed by *AKT1* (~10%) and *PTEN* (~5%). This informed the prevalence in the economic model and financial estimates. However, the prevalence of AKT pathway alterations in the literature is variable (CAPItello-291 reported 40.8% [289/708] AKT pathway altered patients and Park 2024 reported ~60% AKT pathway altered patients) and Australian-specific rates are not known.[7]

Pathogenic variations in the *PIK3CA, AKT,* or *PTEN* (including *PTEN* loss of function) genes can lead to hyperactivation of the AKT signalling cascade resulting in proliferation and tumour progression. The AKT node in the signalling pathway has three isoforms (*AKT1, AKT2,* and *AKT3*) that are key downstream effectors that mediate cell proliferation and resistance to apoptosis. Alterations may present at the time of cancer recurrence and/or may be acquired by means of previous treatment.[8]

CAPI is a novel pyrrolopyrimidine-derived compound, and is a potent, selective ATP-competitive inhibitor of all three AKT isoforms (*AKT 1/2/3*). FULV is an oestrogen receptor down-regulator. CAPI+FULV combination therapy concurrently targets the AKT pathway and oestrogen receptor signalling, resulting in antiproliferative activity in breast cancer cells, and may restore the cancer cells' sensitivity to ET.[9]

The submission proposed that patients whose test results are positive to at least one of *PIK3CA, AKT1,* or *PTEN* alteration are eligible for treatment with CAPI+FULV, while patients whose test results are non-positive (i.e., a negative or unknown test result) are not eligible. In the CAPItello-291 trial, reasons for an unknown test result were due to pre-analytical failure (i.e., testing not performed as the sample did not meet sample quality metrics at pathology review or did not meet wet lab processing quality metrics; 10.3% [73/708]), post-analytical failure (i.e., tumour tissue sample was not evaluable as the sample did not meet bioinformatic quality metrics; 2.7% [19/708]) or the tissue sample was not provided (2% [14/708]).

The commentary noted that PASC confirmed the test population should include patients with the HER2- subtype (which includes the HER2-low subtype [defined as IHC 2+ and ISH-]), who are currently not eligible for HER2 inhibitors (pp5-6, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting). The commentary also noted that the PBAC recommended the listing of trastuzumab deruxtecan (T-DXd) for the treatment of patients with HER2-low unresectable or metastatic breast cancer at the March 2024 PBAC meeting. Therefore T-DXd may be a comparator for a proportion of patients (see Section 8).

The clinical utility standard is the FoundationOneCDx assay, which was used in the pivotal trial, CAPItello-291, for the detection of *PIK3CA, AKT1,* and *PTEN* alterations. FoundationOneCDx is an

[5] Australian Institute of Health and Welfare, Cancer in Australia 2024. 2024, AIHW: Canberra

[6] Howlader, N., et al., US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst*, 2014. 106(5)

[7] Park, L, et al., Testing patterns and prevalence of PIK3CA, AKT1, and PTEN alterations among patients (pts) with HR+/HER2- metastatic breast cancer (mBC) in the US. JCO 42, 1041-1041(2024). DOI: 10.1200/JCO.2024.42.16_suppl.1041

[8] Turner, NC, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. *N Engl J Med* 2023;388:2058-2070; Vol: 388 No: 22. DOI: 10.1056/NEJMoa2214131

[9] Turner, NC, et al. Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer. *N Engl J Med* 2023;388:2058-2070; Vol: 388 No: 22. DOI: 10.1056/NEJMoa2214131

NGS-based IVD device for the detection of substitutions, insertion and deletion alterations (indels) and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability, homologous recombination deficiency, and tumour mutational burden using DNA isolated from FFPE tumour tissue specimens.

The commentary noted that it is not clear how the FoundationOneCDx test compares with other commercial or in-house developed tests. The 1766 Ratified PICO Confirmation (p17) highlighted that it was uncertain whether FoundationOneCDx would be a suitable clinical utility standard, due to its uncertain concordance with such tests. The FDA 2019[10] and FDA 2023[11] reported high concordance from the FoundationOneCDx against an 'externally validated NGS' (FDA 2019: 100% sensitivity/specificity; FDA 2023: 96% sensitivity, 99% specificity); however, the broader applicability of these results was unclear due to the 'externally validated NGS' test not being identified (see Section 12).

As discussed in Section 6, the commentary considered the submission's test population was ambiguous, given the broader scope of the criterion of "following disease progression or recurrence on or after an ET with or without a CDK4/6 inhibitor" compared to that proposed in the PICO confirmation, and also because the proposed positioning of AKT pathway testing in the clinical management algorithm for patients with HR+/HER2- advanced or metastatic breast cancer was unclear.

8. Comparator

The comparator test was 'no testing'. The commentary considered this was reasonable and consistent with the ratified PICO confirmation, in which PASC agreed that the test comparator was no tumour testing for AKT pathway alterations, and advised that there was no subsidised test available to determine AKT pathway alteration status or to guide targeted treatment for patients with HR+/HER2- advanced breast cancer (p15, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting).

The comparator treatment was 2L standard of care (SOC), which the submission nominated to be FULV monotherapy.

The commentary considered the submission's nomination of FULV monotherapy as the only comparator over other 2L SOC therapies was not adequately justified. The commentary noted the choice of comparator is complex, and there are subgroups of patients for whom a different therapy could be the appropriate comparator depending on the previous treatments or other biomarkers. The commentary acknowledged that FULV monotherapy was aligned with the comparator in the pivotal trial; however, no clinical evidence against other comparators (beyond FULV monotherapy) was presented in the submission. The commentary noted that there was a range of potential comparators beyond FULV monotherapy in the 1L, 2L, and 3L settings that may be relevant given that the requested restriction would allow for treatment in the 1L advanced or metastatic setting and beyond.

While the nominated comparator of FULV monotherapy is a relevant 2L therapy, the commentary considered the appropriateness for FULV monotherapy as the main comparator is unclear. The commentary noted that consideration should be given as to whether other 2L SOC therapies, including ET+CDK4 inhibitor, EVE+EXE, olaparib and T-DXd should be considered as part of the comparator given that these therapies would be available as alternatives in some or all of the proposed CAPI+FULV patient population.

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[10] PMA P170019/S006: FDA Summary of Safety and Effectiveness Data
[11] PMA P170019/S048: FDA Summary of Safety and Effectiveness Data

9. Summary of public consultation input

MSAC welcomed consultation input received for this application and noted the period for public consultation closed on 11 October 2024. Noting this was a codependent application, consultation input had also been submitted relating to the PBAC submission, which can be referred to in the PBAC Public Summary Document (PSD) for CAPI following the November 2024 PBAC meeting. Consultation input to MSAC was welcomed from two professional organisations and one consumer group organisation:

- Australian Pathology

- Breast Cancer Network Australia (BCNA)

- Lung Foundation Australia (LFA)

Benefits

The main benefits of public funding provided through the consultation feedback included equitable access to the test. It was noted that current out of pocket costs of this test is between $3,000-$5,000 for individuals.

Respondents agreed on the importance of ensuring treatments are delivered when clinically appropriate, and considered that this test ensures CAPI would be offered to patients as a targeted treatment, which would result in treating those who are likely to receive the most benefit, leading to clinically superior outcomes.

Disadvantages

The consultation input received did not point out any disadvantages with listing this test.

Additional Comments

BCNA noted there are limited treatment options for patients with locally advanced or metastatic HR+/HER2- breast cancer who have developed resistance to endocrine therapies.

Australian Pathology stated that, where a medication may be listed under the PBS, the related genetic test to qualify a patient for that treatment should also be publicly funded.

LFA supported the listing of this test for the proposed breast cancer population; however, it considered that a publicly funded test should also expand the population to include people with non-small cell lung cancer of whom they estimate 3-5% to also have alteration of the HER2 gene. It advocated that comprehensive genomic profiling (CGP) of patients with lung cancer will improve survival and quality of life for patients.

10 Characteristics of the evidence base

The summary of trials/studies informing the linked evidence approach are presented in Table 5.

Table6: Summary of the linked evidence approach

Trial/Study	N	Study design Risk of bias	Population (biomarker)	Intervention/Test	Comparator/Clinical utility standard	Key outcomes	Result used in economic model
Diagnostic accuracy (cross sectional) evidence							
Monash Health Pathology 2024	21	CA High	BC (*PIK3CA/ AKT1/ PTEN* positive only)	Roche AVENIO CGP	F1CDx	PPA, NPA	Not used
FDA 2019	101	CA High	HR+/HER2- LA/M BC (*PIK3CA*)	F1CDx	Externally validated NGS	PPA, NPA	Not used
FDA 2023 *	236	CA Unclear	HR+/HER2- LA/M BC (*PIK3CA/ AKT1/ PTEN*)	F1CDx	Externally validated NGS	PPV, NPV, PPA, NPA	Not used
Prognostic and predictive validity of the biomarker evidence							
CAPItello-291 [a]	708	P3, R, DB, PC, MC Low [b]	HR+/HER2- LA/M BC after progression or after AI +/- CDK4/6 inhibitor (*PIK3CA, AKT1, PTEN*)	CAPI + FULV	Placebo + FULV	PFS, OS, HRQoL, DoR, safety	PFS, OS, HRQoL, safety in Altered population
FAKTION [c]	140	P2, R, DB, PC, MC Low (ITT) [d] High (AKT)	Post-menopausal ER+/HER2- LA/M BC after progression or after AI; CDK4/6 inhibitor-naïve (*PIK3CA, AKT1,[e] PTEN*)	CAPI + FULV	Placebo + FULV	PFS, OS, safety	Not used
SOLAR-1 [f]	572	P3, R, DC, PC, MC Low	Post-menopausal HR+/HER2- LA/M BC before or after progression on ET +/- CDK4/6 inhibitor (*PIK3CA*)	Alpelisib + FULV	Placebo + FULV	PFS, OS, ORR, safety	Not used
BELLE-3 [f]	432	P3, R, DB, PC, MC Low	Post-menopausal HR+/HER2- LA/M BC before or after progression on or after ET + mTOR inhibitor; CDK4/6 inhibitor-naïve (*PIK3CA*)	Buparlisib + FULV	Placebo + FULV	PFS, OS, ORR, safety	Not used

Source: Monash Health Pathology 2024; FDA 2019 report; CAPItello-291, FAKTION, SOLAR-1, BELLE-3; FDA 2023 report

AI = aromatase inhibitor; AKT = serine/threonine kinase; BC = breast cancer; CA = concordance analysis; CAPI = capivasertib; CDK4/6 = cyclin dependent kinase 4 and 6; CGP = comprehensive genomic profiling; DAS = diagnostic accuracy study; DB = double blinded; DoR = duration of response; ET = endocrine therapy; F1CDx = FoundationOneCDx; FDA = Food and Drug Administration; FULV = fulvestrant; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; HRQoL = health related quality of life; ITT = intention to treat; LA/M = locally advanced/metastatic; MC = multicentre; mTOR = mammalian target of rapamycin; NGS = next-generation sequencing; NPA = negative percent agreement; ORR = objective response rate; OS = overall survival; PC = placebo controlled; PFS = progression free survival; PPA = positive percent agreement; P2 = phase 2; P3 = phase 3; R = randomised

* identified during the evaluation

[a] CAPItello-291 informed both the prognostic and predictive validity of AKT pathway alterations.

[b] CAPItello-291 was considered low risk of bias overall, but there was potential for reporting bias given the high proportion of patients with unknown AKT status.

[c] FAKTION informed both the prognostic and predictive validity of AKT pathway alterations.

[d] The ITT cohort in FAKTION was considered low risk, however, the AKT subgroup results were considered to have a high risk of bias given the exploratory *post hoc* nature of these groups

[e] *AKT1* was not analysed in the original study design. *AKT1* testing was conducted at a later date and assessed under the "Expanded" population

[f] SOLAR-1 and BELLE-3 informed the prognostic validity of AKT pathway alterations

Note:

Risk of bias assessment of diagnostic accuracy studies performing using the QUADAS-2 tool; and for randomised controlled trial using the Cochrane risk of bias tool.

The submission did not present formal evidence to demonstrate the change in management given a positive or negative result for AKT pathway alterations.

The submission presented two concordance analyses to inform the diagnostic accuracy of AKT pathway testing: Monash Health Pathology 2024 (N=21; Roche AVENIO vs FoundationOneCDx) and FDA 2019 (N=101; FoundationOneCDx vs 'Externally validated NGS'). The FDA 2023 (N=236;

FoundationOneCDx vs 'Externally validated NGS') report was identified and included during the evaluation.

Four randomised controlled trials (RCTs) were presented to inform the prognostic effect of AKT pathway alterations based on treatment with placebo + FULV: CAPItello-291 (N=708), FAKTION (N=140), SOLAR-1 (N=572), and BELLE-3 (N=432). CAPItello-291 and FAKTION also informed the predictive effect of AKT pathway alterations based on treatment with CAPI+FULV compared to placebo + FULV.

The submission did not provide formal evidence to demonstrate the change in management given a positive or negative result for AKT pathway alteration.

The commentary considered the diagnostic evidence presented was at high risk of bias and/or had limited applicability to the proposed test setting. The Monash Health Pathology 2024 concordance analysis between Roche AVENIO CGP and FoundationOneCDx was based on 16/21 tissue samples, where 24% (5/21) were unsuccessful (mainly due to insufficient DNA yield) on the FoundationOneCDx; however, all samples were known positive for *PIK3CA, AKT1, or PTEN* variants and thus the interpretation of negative concordance was uncertain. PASC previously considered the results from the Monash Health Pathology 2024 report to be uncertain, noting that tumour enrichment data of samples were not provided, *PTEN* deletions were not detected by either test, and FoundationOneCDx did not identify a *PTEN* point variation (p.D268E; p17, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting). Additionally, the commentary considered that both the FDA 2019 (n=101) and FDA 2023 (N=236) reports had reduced applicability to the proposed test setting since FoundationOneCDx was compared against an 'externally validated NGS' that was not specified; FDA 2019 only detected *PIK3CA* alterations; and the FDA 2023 report included tumour tissue samples from metastatic triple negative breast cancer (TNBC) patients.

An overview of the testing characteristics and mutation cohorts in the prognostic and predictive evidence are presented in Table6.

Table 7: Overview of testing characteristics and mutation cohorts in CAPItello-291, FAKTION, SOLAR-1, and BELLE-3

	CAPItello-291	FAKTION	SOLAR-1	BELLE-3
Biomarker tested	*PIK3CA, AKT1,* and *PTEN*	Original protocol: *PIK3CA* and *PTEN* Updated protocol: *PIK3CA, AKT1,* and *PTEN*	*PIK3CA*	*PIK3CA*
Assay used	NGS (F1CDx)	Original: ddPCR, IHC, Expanded: ddPCR, NGS (F1CDx GuardantOMNI RUO) NGS: NGS (F1CDx and GuardantOMNI RUO)	PCR (clinical trial assay and therascreen *PIK3CA* RGQ PCR Kit)	ctDNA (Inostics BEAMing assay), PCR (Roche cobas *PIK3CA* assay)
Sample	Tissue	Tissue and plasma	Tissue	Tissue or plasma
Positive, n/N (%)	289/708 (41)	Original: 59/140 (42) Expanded: 76/140 (54) NGS: 63/140 (45)	341/572 (60)[a]	ctDNA: 135/348 (39)[b] Tissue: 110/320 (34)[c]
Negative, n/N (%)	313/708 (44)	Original: 81/140 (58) Expanded: 64/140 (46) NGS: 49/140 (35)	231/572 (40)[a]	cDNA: 213/348 (61)[b] Tissue: 204/320 (64)[c]
Unknown, n/N (%)	106/708 (15)	-	-	Tissue: 7/320 (2)

Source: constructed during the evaluation from Table 2.4, p33; 2.8, p41; Table 2.12, p48; Table 2.13, p51 of the submission; Table 2, Howell 2022 (FAKTION); Table 1, Di Leo 2018 (BELLE-3); Table 1, Andre 2019 (SOLAR-1)

AKT = serine/threonine kinase; ctDNA = circulating tumour DNA; ddPCR = digital droplet polymerase chain reaction; F1CDx = FoundationOneCDx; IHC = immunohistochemistry; n = number; NA = not applicable; NGS = Next Generation Sequencing; PCR = polymerase chain reaction; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN = phosphatase and tensin homolog

[a] In SOLAR-1 patients were grouped into *PIK3CA* mutated (N=341) or non-*PIK3CA* mutated cohorts (N=231) and then randomised to receive alpelisib + fulvestrant (FULV) (*PIK3CA* mutated = 169; non-*PIK3CA* mutated = 115) or placebo + FULV (*PIK3CA* mutated = 172; non-*PIK3CA* mutated = 116)

[b] the denominator is the available ctDNA samples collected

[c] the denominator is the available tumour tissue samples collected

CAPItello-291: tested for *PIK3CA*, *AKT1*, and *PTEN* using the NGS FoundationOneCDx

FAKTION: tested for PIK3CA, AKT1, or PTEN using three testing protocols: 'Original' AKT pathway altered protocol: digital droplet polymerase chain reaction (ddPCR)/ pyrosequencing and IHC for the detection of PIK3CA and loss of PTEN expression (tissue and blood samples); 'Expanded AKT pathway altered protocol: ddPCR/pyrosequencing and NGS (tissue via FoundationOneCDx and blood samples via GuardantOMNI RUO); and 'NGS-identified AKT pathway altered protocol': NGS (tissue via FoundationOneCDx and blood samples via GuardantOMNI RUO)

SOLAR-1: tested for *PIK3CA* alterations using polymerase chain reaction (PCR) of tumour tissue samples (clinical trial assay and therascreen *PIK3CA* RGQ PCR Kit)

BELLE-3: tested for *PIK3CA* alterations was conducted in circulating tumour DNA (ctDNA; Inostics BEAMing assay) and tumour tissue samples (PCR Roche cobas PIK3CA assay).

In CAPItello-291, FAKTION, SOLAR-1, and BELLE-3, the overall risk of bias was low in the intention to treat (ITT) populations. However, the commentary considered there was an unclear to high risk of bias in the AKT pathway altered subgroups since the analyses of the non AKT pathway altered patients in CAPItello-291, and all AKT pathway subgroups in FAKTION and BELLE-3, were exploratory with some subgroup analyses conducted *post hoc*. The commentary also noted there was potential for performance bias in relation to the reporting of subjective outcome measures (e.g., PFS, health-related quality of life [HRQoL], safety) in the intervention arms (CAPI+FULV, alpelisib+FULV, buparlisib+FULV) given the higher rates of adverse events (AEs) associated with AKT-inhibitors compared to placebo + FULV that might have led to unintentional unblinding of patients.

CAPItello-291 was considered by the commentary to be the most representative of proposed test setting since CAPItello-291 tested for *PIK3CA, AKT1, and PTEN* alterations using the clinical utility standard (FoundationOneCDx) on tumour tissue samples; assessed the comparative effectiveness in patients treated with CAPI+FULV and placebo + FULV; and included patients exposed to CDK4/6 inhibitor therapy (70.1% [496/708]) which may better reflect current clinical practice.

Comparatively, in the original protocol for FAKTION, SOLAR-1, and BELLE-3, the testing procedures differed to the proposed test setting (e.g., tests conducted using polymerase chain reaction [PCR] assay or IHC; tested tumour tissue and/or blood samples; tested for *PIK3CA* gene variants only). FAKTION categorised patients by AKT pathway status using three different methods and this potentially led to the same patient being categorised as AKT pathway altered in one approach but non altered in another. The updated protocol in FAKTION included testing with FoundationOneCDx but this was a *post hoc* analysis, and the results were considered potentially uncertain by the commentary. Furthermore, the commentary noted the evaluation of efficacy in the AKT pathway altered subgroups was only included as secondary or exploratory analyses, and adjustments for multiplicity were not performed. Hence, subgroup data analyses based on AKT pathway alteration status reported in FAKTION, SOLAR-1 and BELLE-3 were considered to be of limited applicability and value by the commentary to inform the prognostic and predictive validity of AKT pathway testing using NGS.

However, the commentary considered that despite CAPItello-291 being considered as applicable to the test setting and the AKT pathway altered subgroup being a primary analysis group, the complement subgroup analysis (i.e., the non AKT pathway altered subgroup that included 'known non AKT pathway altered' and 'unknown AKT status') was treated as exploratory in the trial. As such, there is some uncertainty around the interpretation of results from the complement, in particular when informing the tests for interaction to identify a significant treatment effect modifier (see Section 12).

Further, the commentary noted there were potential applicability issues from CAPItello-291 to Australian clinical practice. For example, ~13% (89/708) had no prior lines of therapy (ET and chemotherapy) for locally advanced or metastatic disease while ~25% (176/708) had two or three prior lines of therapy for locally advanced or metastatic disease, and ~30% (212/708) were CDK4/6 inhibitor-naïve. Placebo + FULV may not be the relevant comparator for these patients in clinical practice (see Section 12). The commentary also considered it was unclear that placebo + FULV was representative of 2L treatment in all patients with the landscape of treatment changing. Therefore, the prognostic and predictive effect of AKT pathway alterations as informed by treatment with placebo + FULV and CAPItello-291 may have limited applicability to the target population in the Australian clinical practice.

10. Comparative safety

Adverse events from testing

The submission did not present any formal safety evidence for AKT pathway testing.

The submission (p87) stated that re-testing and/or re-biopsy may be required in some patients after disease progression. Fresh biopsies are preferred but archival tissue can be used (e.g., for bone or brain metastases). The submission assumed that if a new tumour tissue sample is required, the risk/benefit profile of tumour biopsy would be assessed and managed by radiologists, surgeons, oncologists and pathologists. The submission considered that testing of AKT pathway alterations (*PIK3CA, AKT1* or *PTEN*) is not expected to introduce any additional safety concerns to patients.

The commentary considered this claim may not be reasonable since:

- Under the current MBS item descriptor, testing can occur in *de novo* advanced or metastatic patients; however, under the requested PBS restriction, treatment with CAPI+FULV is only allowed after disease progression or recurrence. Patients who initially test non-positive but may develop an AKT pathway alteration after disease progression are potentially tested twice before receiving treatment with CAPI+FULV. If fresh tissue samples are taken for each test, this presents an additional safety risk for patients.

- It was not clear if a patient whose tumour tissue fails testing could undergo a re-test. Acknowledging the current MBS item descriptor permits only one test per primary tumour

diagnosis, if re-testing is allowed for these patients, given insufficient tumour tissue is available from the initial sample or fresh tissue is preferred, then re-biopsy would be required, which introduces additional risk to the patient.

Adverse events from changes in management

The commentary considered there may be harms associated with tests that yield no result, a false positive, or a false negative result, which the submission did not consider. The commentary noted that re-testing (or the absence of re-testing) would delay time to receiving optimal treatment, and false positive and negative results could lead to patients receiving inappropriate treatment and/or experiencing unnecessary adverse events (AE). The commentary also noted the FDA 2023 report stated that high concordance of the test may mitigate these risks (p47-8, FDA 2023, 'PMA P170019/S048: FDA Summary of Safety and Effectiveness Data'); however, the concordance of testing was uncertain as the actual NGS test which will be used in practice was unknown and the rate of false positive and negative results are considered uncertain and not well informed by the available evidence (see Section 12).

11. Comparative effectiveness

The data available to inform the effectiveness of the test and treatment are presented in Table 7.

Table 8: Data availability to inform comparisons

Proposed test vs no test	No evidence provided	
Proposed test vs alternative test	Monash Health Pathology 2024 concordance analysis between Roche AVENIO CGP and FoundationOneCDx. Supplementary concordance analysis between FoundationOneCDx and an externally validated NGS (FDA 2019 and FDA 2023).	
	CAPI+FULV	**FULV monotherapy**
Biomarker test positive	CAPItello-291, FAKTION	CAPItello-291, FAKTION
Biomarker test negative	CAPItello-291, FAKTION	CAPItello-291, FAKTION

Source: Section 2A, 2B, 2C, and 2D of the submission
CGP = Comprehensive Genomic Profiling; FDA = Food and Drug Administration; NGS = Next Generation Sequencing

Comparative accuracy/test performance

The concordance results from the Monash Health Pathology 2024 and FDA 2019 reports are presented in Table 8. The FDA 2023 results were included during the evaluation and are presented in Table 9.

Table 9: Concordance summary Monash Health Pathology 2024 and FDA 2019

Monash Health Pathology 2024 Roche AVENIO CGP vs FoundationOneCDx		FoundationOneCDx		
		Positive	Negative	Total
Roche AVENIO CGP	Positive	**redacted**	**redacted**	**redacted**
	Negative	**redacted**	**redacted**	**redacted**
	Total	**redacted**	**redacted**	
Agreement (95% CI)	PPA	**redacted**%		
	NPA	**redacted**%		
FDA 2019 **FoundationOneCDx vs Externally validated NGS**		**Externally validated NGS**		
		Positive	Negative	Total
FoundationOneCDx	Positive	53	0	53
	Negative	0	48	48
	Total	53	48	101
Agreement (95% CI)	PPA	100% (93.3 – 100)		
	NPA	100% (92.6 – 100)		

Source: Table 2.19, p65 of the submission; Table 2.25, p72 of the submission
CGP = Comprehensive Genomic Profiling; CI = confidence interval; NGS = Next Generation Sequencing; NR = not reported;
NPA=Negative percent agreement; PPA=Positive percent agreement
Note: The submission stated that 5 cases were not successful on the FoundationOneCDx assay (although Roche AVENIO CGP could produce a valid result).

Table 10: Concordance results of FoundationOneCDx against 'externally validated NGS' (reference standard) for the detection of AKT1/PIK3CA/PTEN - FDA 2023 (variant-level).

FDA 2023 FoundationOneCDx vs Externally validated NGS		Externally validated NGS (reference standard)			
		Positive	Negative	Invalid	Total
FoundationOneCDx	Positive	144	9	1	154
	Negative	6	13,529	57	13,592
	Invalid	0	0	0	0
	Total	150	13,538	58	13,746
Agreement (95% CI)	PPA	96% (91.55, 98.15)			
	NPA	99.93% (99.87, 99.97)			
Predictive value (95% CI)	PPV	94.12% (89.2, 96.87)			
	NPV	99.96% (99.9, 99.98)			

Source: Table 13, p23 https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S048B.pdf
CI = confidence interval; NGS = Next Generation Sequencing; NPA=Negative percent agreement; NPV = negative predictive value;
PPA=Positive percent agreement; PPV = positive predictive value

Monash Health Pathology 2024 reported a 100% concordance rate across 16/21 samples and a correlation rate of 0.8901. The results for **redacted** samples could not be obtained from FoundationOneCDx. However, the submission stated that for these five cases there was a high concordance between Roche AVENIO CGP and the accredited in-house TST70 gene panel supplied by Illumina. No negative samples were tested and therefore the accuracy for testing negative results could not be informed by the Monash Health Pathology 2024 study.

As noted in Section 10, the commentary noted the Monash Health Pathology 2024 evidence appeared unchanged from that considered by the PASC in April 2024, which considered the concordance results to be uncertain. In regard to the Illumina TST70 gene panel, the PASC additionally noted that the Illumina TST70 panel seemed to target hotspot sequence variants only and did not identify or intend to identify deletion (p17, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting). The commentary considered it was unclear if the TST70 was a valid standard to be comparing the Roche AVENIO test against; the differences in the detected gene variants by the TST70 compared to the proposed test and clinical utility standard highlights potential variability across other in-house NGS.

The FDA 2019 reported 100% concordance between FoundationOneCDx and an 'externally validated NGS' for the detection of *PIK3CA* alterations. The FDA 2023 reported 96% and 99% PPA and NPA, respectively, in FoundationOneCDx against an 'externally validated NGS' for the detection of *PIK3CA, AKT1,* and *PTEN* alterations.

The commentary noted that both FDA reports had reduced applicability to the proposed test setting and, regardless, the concordance between the Roche AVENIO CGP or 'other in-house NGS' expected to be used in practice against the FoundationOneCDx remains uncertain.

Prognostic evidence

The PFS and OS results in the placebo + FULV arms from CAPItello-291, FAKTION, SOLAR-1, and BELLE-3 are presented in Table 10.

Table 11: Summary of PFS and OS according to AKT pathway alteration status in the SOC arms of CAPItello-291, FAKTION, SOLAR-1, and BELLE-3

Study ID	Biomarker subgroup	Biomarker analysis	Median PFS, months (95% CI)		Median OS, months (95% CI)	
			Altered pathway	Non-altered pathway	Altered pathway	Non-altered pathway
CAPItello-291 (N=353)	*PIK3CA/AKT1/PTEN*	NGS	3.1 (2, 3.7)	3.7 (3, 5) [a] 3.7 (3.5, 5.1) [b]	NE (20.3, NE)	NE (21.3, NE) [a]
FAKTION (N=71)	*PIK3CA/PTEN* (Original)	ddPCR, IHC	5.2 (3.1, 8.4)	4.8 (3.0, 10.3)	20.9 (15.5, 36.1)	23.9 (16.3, 33.3)
	PIK3CA//AKT1/PTEN (Expanded)	ddPCR, IHC, NGS	4.6 (2.8, 7.9)	4.9 (3.2, 10.5)	20 (14.8, 31.4)	25.2 (20.3, 36.2)
	PIK3CA//AKT1/PTEN (Expanded)	NGS	3.1 (2.8,7.7)	5.2 (2.2, 10.5)	20.9 (14.1, 35.4)	25.2 (15.3, 38.8)
SOLAR-1 (N=288)	*PIK3CA*	PCR	5.7 (3.7, 7.4)	5.6 (3.9, 9.1)	31.4 (26.8, 41.3)	NR
BELLE-3 (N=143)	*PIK3CA*	ctDNA	1.6 (1.4, 2.8)	2.7 (1.5, 3.6)	NR [c]	NR [c]
	PIK3CA	PCR	1.4 (1.4, 2.2)	1.7 (1.4. 2.9)	NR [c]	NR [c]

Source: adapted from Table 2.15, pp56-7 of the submission; Andre 2020 (SOLAR-1 updated OS results)
AKT = serine/threonine kinase; ctDNA = Circulating tumour DNA; ddPCR = digital droplet polymerase chain reaction; IHC = immunohistochemistry; N = number of patients in the comparator arm; NE = Not estimable NGS = Next-Generation Sequencing; NR = not reported; OS = overall survival; PCR = Polymerase chain reaction; PFS = progression free survival; PIK3CA = phosphatidylinositol 3-kinase; PTEN = Phosphatase and tensin homolog; SOC = standard of care (placebo + fulvestrant)
* n/N represents the proportion of altered or non-altered patients in the comparator arm from each respective trial
[a] in patients with non AKT pathway altered tumours (including unknown patients)
[b] in patients with known non AKT pathway altered tumours (excluding unknown patients)
[c] the submission stated that due to early study termination OS data collection stopped early. As such, final OS analyses was not completed in BELLE-3
Median follow up durations in the comparator arms of each trial were:
CAPItello-291 14.3 months; FAKTION 62.3 months; SOLAR-1 at data cutoff December 23, 2016, 20 months in the *PIK3CA* altered cohort and 7.4 months in the non-*PIK3CA* altered cohort and at data cutoff April 23, 2020, 42.4 months in the *PIK3CA* altered cohort and was not reported for the non-*PIK3CA* altered cohort; BELLE-3 12 months

The submission stated that AKT pathway altered tumours had a low prognostic impact among patients with HR+/HER2- locally advanced or metastatic breast cancer treated with SOC (placebo + FULV), since the median PFS was similar between AKT pathway altered and non AKT pathway altered subgroups in each respective trial. Although inconsistent with the claims made in the clinical evidence, the submission (p7) also considered that "patients with alterations in this pathway may experience rapid disease progression and worse clinical outcomes".

Overall, the commentary considered that the evidence presented to inform the prognostic effect of AKT pathway alterations was highly uncertain, and it was not clearly supportive of any prognostic effect nor was strong evidence provided to support any claims regarding the magnitude of any effect, since:

- The median PFS between AKT pathway altered and (known) non AKT pathway altered patients varied across trials (e.g. in altered pathway, ranged from 1.4 months in BELLE-3 using PCR to 5.2 months in FAKTION using digital droplet polymerase chain reaction [ddPCR], IHC).There was no clear signal of a prognostic effect, given that the median PFS in the AKT pathway altered and non AKT pathway altered subgroups within each trial showed overlapping 95% CIs.

21

- While CAPItello-291 was considered more applicable to the proposed test setting than FAKTION, SOLAR-1 and BELLE-3, patients in CAPItello-291 were not randomised by AKT pathway alteration status, and the non AKT pathway altered subgroups were exploratory *post hoc* analyses, and so results from these subgroups are interpreted with caution. The FAKTION, SOLAR-1, and BELLE-3 trials also analysed AKT pathway subgroups in an exploratory manner and had limited applicability to the proposed test setting (e.g., used different assays; tested tumour tissue and/or blood samples; tested different gene variants).

- The applicability of interpreting the prognostic effect of AKT pathway testing based on treatment with placebo + FULV is reduced given there is no established 2L SOC in Australia and the clinical landscape for 2L HR+/HER2- locally advanced metastatic breast cancer is evolving.

The presented evidence supporting the prognostic effect of AKT pathway alterations was considered equivocal by the commentary. However, the commentary noted that in CAPItello-291 (which primarily informed the predictive effect of AKT pathway testing) there was a lower median PFS in the AKT pathway altered compared to the known non AKT pathway altered subgroups (3.1 vs 3.7 months), potentially suggesting a worse PFS in AKT pathway altered patients. If AKT pathway alterations were prognostic, this observed difference may be reasonable. Conversely, if AKT pathway alterations were not prognostic, then this lower median PFS in the AKT pathway altered subgroup relative to the known non AKT pathway altered subgroup may suggest an overestimated comparative treatment effect of CAPI+FULV and placebo + FULV in the AKT pathway altered subgroup or an underestimated treatment effect in the known non AKT pathway altered subgroup. As such, the predictive value of treatment with CAPI+FULV in CAPItello-291 was potentially overestimated.

Predictive evidence

The AKT pathway alteration subgroups from CAPItello-291 and FAKTION that informed the predictive effect of AKT pathway testing and treatment with CAPI+FULV are presented in Table 11.

Table 12: AKT pathway alteration subgroups informing the predictive effect of AKT pathway testing

AKT pathway subgroups	CAPItello-291
AKT pathway altered (n=289)	Patients with at least one qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration as detected by NGS F1CDx
Non AKT pathway altered (n=419)	Patients without a qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration including those who are confirmed Known non AKT pathway altered and unknown AKT status as detected by NGS F1CDx
Known non AKT pathway altered (n=313) (included in the 'non AKT pathway altered' subgroup)	Patients confirmed to be without a qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration as detected by NGS F1CDx, excluding patients with unknown AKT pathway status
Unknown AKT pathway status (n=106) (included in the 'non AKT pathway altered' subgroup)	Patients who have an unknown AKT pathway test result due to: • Pre-analytical failure (test not performed due to low quality or insufficient sample) (10.3%, 73/708) • Post-analytical failure (sample was not evaluable) (2.7%, 19/708) • Test sample not provided (2%, 14/708)
	FAKTION
AKT pathway altered: Original protocol (n=59)	Patients with at least one qualifying *PIK3CA* or *PTEN* alteration as detected by ddPCR or IHC
AKT pathway altered: Expanded protocol (n=76)	Patients with at least one qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration as detected by ddPCR and NGS (F1CDx and GuardantOMNI RUO)
AKT pathway altered: NGS only protocol (n=63)	Patients with at least one qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration as detected by NGS only (F1CDx and GuardantOMNI RUO)
Non AKT pathway altered: Original protocol (n=81)	Patients without a qualifying *PIK3CA* or *PTEN* alteration as detected by ddPCR or IHC
Non AKT pathway altered: Expanded protocol (n=52)	Patients without a qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration as detected by ddPCR and NGS (F1CDx and GuardantOMNI RUO)
Non AKT pathway altered: NGS only protocol (n=49)	Patients without a qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration as detected by NGS only (F1CDx and GuardantOMNI RUO)

Source: Table 13, p102 CAPItello-291 CSR; p3-4 Howell 2022 FAKTION
AKT = serine/threonine kinase; ddPCR = digital droplet polymerase chain reaction; F1CDx = FoundationOneCDx; IHC = immunohistochemistry; n = number of patients from the total cohort; NGS = Next Generation Sequencing; PCR = polymerase chain reaction; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN = phosphatase and tensin homolog

The PFS results comparing CAPI+FULV and placebo + FULV in AKT pathway altered and non AKT pathway altered subgroups in CAPItello-291 and FAKTION are presented in Table 12.

Table 13: Overview of PFS in CAPItello-291 and FAKTION

Population	CAPI+FULV		PBO+ FULV		HR (95% CI); p-value [a,b]
	PFS event n/N (%)	Median PFS, months (95%CI)	PFS event n/N (%)	Median PFS, months (95%CI)	
CAPItello-291					
ITT (N=708)	258/355 (72.7)	7.2 (5.5, 7.4)	293/353 (83)	3.6 (2.8, 3.7)	**0.60 (0.51, 0.71); <0.001**
AKT pathway altered (n=289)	121/155 (78.1)	7.3 (5.5, 9.0)	115/134 (85.8)	3.1 (2, 3.7)	**0.50 (0.38, 0.65); <0.001**
Non AKT pathway altered (includes unknown) (n=419)[c]	137/200 (68.5)	7.2 (4.5, 7.4)	178/219 (81.3)	3.7 (3, 5)	0.70 (0.56, 0.88); NR
Known non AKT pathway altered (n=313)	103/142 (72.5)	5.3 (3.6, 7.3)	141/171 (82.4)	3.7 (3.5, 5.1)	0.79 (0.61, 1.02); NR
Unknown AKT result (n=106)	34/58 (58.6)	10 (7.3, 11.1)	37/48 (77)	1.9 (1.8, 7.3)	0.52 (0.32, 0.83); NR
Test for interaction [d]					
AKT pathway altered vs non AKT pathway altered (Complement)					*p=0.0602*
AKT pathway altered vs Known non AKT pathway altered (excludes unknown)					***p=0.0158 [e]***
FAKTION					
ITT (N=140)	54/69 (78)	10.3 (5, 13.4)	64/71 (90)	4.8 (3.1–7.9)	**0.56 (0.38, 0.81); 0.0023**
AKT pathway altered					
Original pathway altered (n=59)	26/31 (83)	10.5 (6.6, 18.7)	28/28 (100)	5.2 (3.1, 8.4)	0.47 (0.26, 0.84); 0.011
Expanded pathway altered (n=76)	30/39 (77)	12.8 (6.6, 18.8)	36/37 (97)	4.6 (2.8, 7.9)	0.44 (0.26, 0.72); 0.0014
NGS-identified pathway altered (n=63)	25/34 (74)	13.4 (6.6, 20.7)	29/29 (100)	3.1 (2.8, 7.7)	0.36 (0.20, 0.65); 0.0007
Non AKT pathway altered					
Original pathway non-altered (n=81)	28/38 (74)	10.3 (3.2, 13.5)	36/43 (84)	4.8 (3.0, 10.3)	0.59 (0.35, 0.98); 0.042
Expanded pathway non-altered (n=64)	24/30 (80)	7.7 (3.1, 13.2)	28/34 (82)	4.9 (3.2, 10.5)	0.70 (0.40, 1.25); 0.23
NGS-identified pathway non-altered (n=49)	18/22 (82)	4.8 (1.3, 10.3)	22/27 (81)	5.2 (2.2, 10.5)	0.95 (0.49, 1.82); 0.87
Test for interaction conducted in FAKTION and during the evaluation					
'Original' AKT pathway altered vs non AKT pathway altered (Complement) [f]					*p=0.18*
'Expanded' AKT pathway altered vs non AKT pathway altered (Complement) [d]					*p=0.2337*
'NGS' AKT pathway altered vs non AKT pathway altered (Complement) [f]					***p=0.046 [e]***

Source: adapted from Table 2.31, p82; Table 2.33, p85; Table 2.72, p151 of the submission

CAPI = capivasertib; CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intention to treat; n = number of participants reporting data; N = total participants in group; NGS = next generation sequencing; NR = not reported; PBO = placebo; PFS = progression free survival

[a] 2-sided p-value. Stratified log-rank test. FAKTION was only powered to detect differences in the ITT population and did not adjust for multiplicity.

[b] stratified Cox proportional hazards model. A hazard ratio <1 favours capivasertib + fulvestrant. In CAPItello-291, for the Overall Population, the log-rank test and Cox model are stratified by presence of liver metastases (yes vs no), prior use of CDK4/6 inhibitors (yes vs no) and geographic region (Region 1: United States, Canada, Western Europe, Australia and Israel, Region 2: Latin America, Eastern

Europe and Russia vs Region 3: Asia). In FAKTION HR was adjusted for pathway status, primary or secondary aromatase inhibitor resistance, and measurable and non-measurable disease.

[c] the non AKT pathway altered population comprised of the Known non AKT pathway altered Population and the Unknown AKT result population

[d] *Test for interaction conducted during the evaluation*

[e] p value < 0.05 suggesting that AKT pathway alteration status was a potentially significant treatment effect modifier

[f] Test for interaction was conducted in FAKTION

Progression determined by RECIST v1.1.

Bold text indicates a statistically significant result (p<0.05). In FAKTION, the HRs for the AKT pathway subgroups were not adjusted for multiplicity and therefore the HRs that appear to be statistically significant (p<0.05) are left un-bolded.

Note:

In CAPItello-291 at DCO1 15 August 2022 the median follow up was 14.9 months CAPI+FULV arm and 14.3 months PBO+FULV arm

In FAKTION, at DCO 25 November 2021 the median follow up was 58.5 months in CAPI+FULV arm and 62.3 months in PBO+FULV arm

CAPItello-291

In CAPItello-291, at the data cutoff 1 (DCO1;15 August 2022), in the ITT population the median duration of follow-up was 14.9 months in the CAPI+FULV arm and 14.3 months in the placebo + FULV arm, and in the AKT pathway altered population was 14.4 months in the CAPI+FULV arm and 13.8 months in the placebo + FULV arm.

CAPItello-291 showed a statistically significant PFS improvement in the CAPI+FULV arm compared to the placebo + FULV arm in the ITT cohort (hazard ratio [HR]=0.60, 95% CI 0.51, 0.71, p<0.001) and the AKT pathway altered subgroup (HR=0.5, 95% CI: 0.38-0.65, p<0.001). There were also point estimate PFS improvements favouring CAPI+FULV over placebo + FULV in the non AKT pathway (HR=0.7, 95% CI 0.56, 0.88) and unknown AKT status subgroups (HR=0.52, 95% CI 0.32, 0.83). When the unknown results were excluded from the non AKT pathway altered subgroup, resulting PFS HR in the known non AKT pathway altered subgroup was 0.79 (95% CI 0.61, 1.02) and included the null.

The commentary noted that PFS results from CAPItello-291 suggested that AKT pathway altered patients had a greater PFS improvement compared to known non AKT pathway altered patients after treatment with CAPI+FULV (median PFS 7.3 vs 5.3 months). The commentary considered this may be indicative of a predictive effect from AKT pathway altered after treatment with CAPI+FULV when compared to placebo + FULV and this was also noted by the PASC (p11, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting).

A key issue identified by the commentary is that the actual complement to the AKT pathway altered subgroup in clinical practice are patients without a positive AKT pathway alteration result - represented in CAPItello-291 by the non AKT pathway altered subgroup that includes patients from both known non AKT pathway altered and the unknown AKT pathway status subgroups. The commentary considered that since the proposed test and treatment algorithm did not require these two subgroups to be treated separately, it would be unreasonable to ignore the results of the unknown AKT pathway alteration subgroup in the consideration of the predictive validity of the biomarker using the clinical utility standard. The actual complement to the requested population of AKT pathway altered was the non AKT pathway altered subgroup, which reported a PFS HR that also favoured CAPI+FULV (PFS HR = 0.70, 95% CI 0.56, 0.88) and as such it may not be reasonable to exclude these patients from treatment.

As noted in Section 10, the commentary noted this should be considered alongside the analyses of known non AKT pathway altered and unknown AKT status subgroups being exploratory analyses conducted *post hoc* and not adjusted for multiplicity. The results in the unknown subgroup were noted by the commentary to be more favourable towards CAPI+FULV (median PFS 10 months) and less favourable towards placebo + FULV (median PFS 1.9 months) compared to the PFS in the other AKT pathway subgroups. Even under the assumption that all patients with an unknown result were AKT pathway altered, the commentary noted the magnitude of the difference in median PFS was not consistent with the results from the AKT pathway altered subgroup in either arm. For example, the median PFS of the AKT pathway altered subgroup compared to the unknown AKT status subgroup in the CAPI+FULV arm was 7.3 and 10 months, respectively; and in the placebo +

FULV arm was 3.1 and 1.9 months, respectively. However, this variation could be due to chance given the smaller sample size of this subgroup.

Tests for interaction conducted during the evaluation suggested a significant treatment effect modifier (p=0.0158) in the AKT pathway altered and known non AKT pathway altered subgroups (excluding unknown AKT status); but not in the AKT pathway altered and the true complement (p=0.0602). The commentary considered it unreasonable to exclude results of the unknown AKT pathway altered patients from the complement when they would be part of the complement in clinical practice; however, this may have arisen from the imperfect testing procedures of the clinical utility standard (FoundationOneCDx) resulting in a considerable number of unknown results (15% of CAPItello-291) rather than the lack of predictive value of the biomarker.

FAKTION

In FAKTION, at the DCO (25 November 2021) the median follow up was 58.5 months in the CAPI+FULV arm and 62.3 months in the placebo + FULV arm.

In FAKTION, a point estimate PFS benefit was observed in the AKT pathway altered patients identified using the 'Original' protocol (PFS HR = 0.47, 95% CI 0.26, 0.84); the 'Expanded' protocol (PFS HR = 0.44, 95% CI 0.26, 0.72); and the 'NGS-identified' protocol (PFS HR=0.36, 95% CI 0.2, 0.65). In the non AKT pathway subgroups, only the 'Original' subgroup showed a PFS benefit (PFS HR = 0.59, 95% CI 0.35, 0.98); the PFS HR in the 'Expanded' (PFS HR=0.7, 95% CI 0.4, 1.25) and 'NGS-identified' subgroups (PFS HR=0.95, 95% CI 0.49, 1.82) included the null.

The commentary considered the results from FAKTION may suggest that patients who are AKT pathway altered as identified by NGS may have improved PFS and OS benefit from CAPI+FULV compared to placebo + FULV; and there may be no additional benefit from CAPI+FULV in NGS identified non AKT pathway altered patients. A test for interaction conducted during the evaluation in FAKTION suggested a significant treatment effect modifier in the 'NGS-identified' AKT pathway altered subgroup. However, results are interpreted with caution as the sample sizes informing these subgroups were small; the 'Expanded' and 'NGS-identified' AKT pathway subgroups were included as exploratory *post hoc* analyses, which alongside tests for interaction, were not adjusted for multiplicity; and NGS testing was conducted in tissue (FoundationOneCDx) and plasma (GuardantOMNI RUO) samples and the predictive effect from detecting alterations from either method could not be differentiated which reduces the applicability of results to the proposed test setting.

Overall, the commentary noted it was likely that CAPI+FULV was more effective than placebo + FULV in AKT pathway altered patients. However, based on available evidence, the efficacy (or lack thereof) in patients without a positive AKT pathway alteration was less clear and therefore it was not immediately apparent that patients from the true complement subgroup should be excluded from CAPI+FULV treatment. The commentary noted that in CAPItello-291, results in the complement subgroup (i.e., non AKT pathway altered and unknown patients) suggested that CAPI+FULV may be more effective than placebo + FULV (95% CI does not include 1.0) and that AKT pathway alteration was not a treatment effect modifier (p=0.0602). In FAKTION, the lack of multiplicity adjustment and different results from test for interaction depending on the testing methods also increased the uncertainty of the subgroup results.

Change in management in practice

The submission did not present any formal evidence to inform change in clinical management for patients identified as having a AKT pathway alteration (*PIK3CA, AKT1, PTEN*). The submission appeared to make a number of assumptions about the change in clinical management based on results from the concordance evidence (Monash Health Pathology 2024) and CAPItello-291. The commentary noted that CAPItello-291 was relied upon to inform co-dependency between AKT pathway testing and treatment with CAPI+FULV. However, in CAPItello-291, patients received CAPI+FULV or placebo + FULV irrespective of their AKT pathway alteration status, and therefore

this did not explicitly inform changes in clinical management. The TGA indication for CAPI+FULV also did not limit treatment to patients with an AKT pathway alteration.

The commentary noted the requested test and treatment population were locally advanced (inoperable) or metastatic HR+/HER2- breast cancer following recurrence or progression on or after ET, with or without a CDK4/6 inhibitor. The proposed MBS item descriptor and requested PBS restriction suggest that testing and treatment with CAPI+FULV occur at the 1L and beyond advanced or metastatic setting, although the description in the submission (e.g. p89) suggest that CAPI+FULV may be used in 1L or 2L. However, the commentary noted that the PASC previously considered that testing is mainly for assessing eligibility for 2L treatment with CAPI+FULV. Additionally, the commentary noted that PASC considered patients who have previously undergone germline *PTEN* testing (via MBS 73296 and 73297) would also be eligible for AKT pathway testing for somatic gene variants, and that testing positive to germline *PTEN* testing may not be sufficient to establish eligibility for CAPI+FULV.

The commentary noted the Roche AVENIO CGP is the proposed test, however, it was not clear whether this test would be used in clinical practice as the submission (p60) noted that other in-house accredited IVD NGS gene panels could be used for the detection of *PIK3CA, AKT1,* or *PTEN* alterations. Overall, the commentary considered it was unclear if testing of AKT pathway alterations using the Roche AVENIO CGP or other in-house NGS assays that may be used for the detection of *PIKC3A, AKT1*, and *PTEN* gene variants in Australian clinical practice would identify the same patients as the clinical utility standard, FoundationOneCDx. This is due to the uncertainty around the results of the main concordance study (Monash Health Pathology 2024) as well as uncertainty around which tests will actually be used in Australia.

The commentary acknowledged that the clinical evidence from CAPItello-291 suggested that patients who have a confirmed AKT pathway altered tumour derive a PFS benefit from treatment with CAPI+FULV compared to placebo + FULV; but the PFS HR in patients who have known non AKT pathway altered tumours included the null in the 95% confidence interval. However, the commentary noted the PFS HR in the true complement to positive AKT pathway altered patients (i.e., known non AKT pathway altered and unknown AKT pathway status subgroups) suggested that CAPI+FULV was still effective and therefore it may not be reasonable to exclude patients who were not classified as confirmed AKT pathway altered from treatment with CAPI+FULV.

Tests for interaction conducted during the evaluation suggested that AKT pathway alteration status was a potentially significant PFS treatment effect modifier. However, this was considered alongside the fact that the PFS data that informed the predictive effect of AKT pathway alterations was exploratory data; and there was uncertainty in the prognostic effect of AKT pathway alterations that may have overestimated the predictive effect.

As such, the commentary contends there remains uncertainty to unequivocally exclude patients who did not test positive to AKT pathway alteration from treatment with CAPI+FULV. In fact, the submission (p89) proposed that these patients would benefit from and therefore elect for treatment with CAPI+FULV, though this was inconsistent with the claims made throughout the submission. The submission did not describe the clinical pathway for patients who receive 'no result' or a false result from testing, which was not reasonable as mismanagement of these patients poses a risk of wastage and safety concerns for patients (e.g., re-testing, re-biopsy, delayed time to treatment, or sub-optimal treatment delivered).

The commentary noted the TGA approved indication allows for treatment with CAPI+FULV irrespective of AKT pathway alteration status. However, the TGA Delegate Overview had reservations with respect to the uncertainty in the point estimate benefit observed in the known non AKT pathway altered subgroup and the higher rates of complications associated with CAPI+FULV.

Notably, the commentary noted there was no statistically significant OS benefit demonstrated between CAPI+FULV and placebo + FULV in the ITT cohort or any of the AKT pathway alteration subgroups in CAPItello-291 at the latest data cut. The commentary acknowledges the immaturity

of OS data in CAPItello-291; the current evidence suggests that irrespective of AKT pathway alteration status, there is no significant OS benefit observed from CAPI+FULV in patients with HR+/HER2- locally advanced or metastatic breast cancer.

Claim of codependence

The commentary considered the evidence informing the diagnostic accuracy of the Roche AVENIO CGP and the FoundationOneCDx for the detection of *PIK3CA, AKT1,* or *PTEN* alterations was highly uncertain as:

- The Monash Health Pathology 2024 report was a concordance analysis based on 16/21 tissue samples, where **redacted**% were unsuccessfully tested on the FoundationOneCDx; all samples were known positive for *PIK3CA, AKT1,* or *PTEN* variants and thus the interpretation of negative concordance was uncertain. PASC previously considered the results from Monash Health Pathology 2024 report to be uncertain, noting that tumour enrichment data of samples were not provided, *PTEN* deletions were not detected by either test, and FoundationOneCDx did not identify a *PTEN* point variation (p.D268E)*.

- There were applicability concerns in the Food and Drug Administration (FDA) 2019 and FDA 2023 concordance analyses, because the FDA 2019 report only tested for *PIKC3CA* gene variants; the FDA 2023 report included tumour tissue samples from patients with metastatic triple negative breast cancer (TNBC); and neither FDA report specified the externally validated next-generation sequencing (NGS) test used.

- It was not clear whether the Roche AVENIO CGP would be the test adopted in Australian clinical practice since the submission noted that other in-house NGS *in vitro* diagnostic (IVD) devices could be used for AKT pathway testing. Importantly, it was not clear whether in-house IVD NGS would be standardised for AKT pathway testing to account for variability across laboratories.

The commentary considered the evidence supporting the prognostic effect of AKT pathway alterations was also uncertain and it was not clearly apparent whether a prognostic effect existed or could be reasonably quantified because:

- The median PFS between AKT pathway altered and non AKT pathway altered patients varied across trials (e.g. in altered pathway, ranged from 1.4 months in BELLE-3 using polymerase chain reaction [PCR] to 5.2 months in FAKTION using droplet digital PCR [ddPCR] or immunohistochemistry [IHC]) and there was no clear signal of a prognostic effect with the median PFS in the AKT pathway altered and non AKT pathway altered subgroups within each trial showed overlapping 95% confidence intervals (CIs).

- The non AKT pathway altered subgroup from CAPItello-291, and the AKT pathway altered subgroups from FAKTION, SOLAR-1, and BELLE-3, were exploratory *post hoc* analyses.

- FAKTION, SOLAR-1, and BELLE-3 lacked applicability to the proposed test setting (e.g., used different assays [PCR, IHC, or NGS], tested tumour tissue and or blood samples; tested different gene variants [tested *PIK3CA, AKT1* and *PTEN* gene variants or *PIK3CA* gene variants only]).

The pre-sub-committee response (PSCR) (p5-6) noted that as this co-dependent submission requests an MBS listing testing of AKT pathway alterations by NGS in tumour tissue to inform access to PBS subsidised capivasertib in combination with fulvestrant (CAPI + FULV) the impact of the prognostic effect of AKT pathway alterations is of less relevance.

The commentary noted that PASC previously considered that AKT pathway testing appeared to predict response in patients treated with CAPI+FULV based on PFS results from CAPItello-291 and FAKTION. CAPItello-291 and FAKTION indicated a greater PFS improvement in AKT pathway altered patients compared to non AKT pathway altered patients, and tests for interaction suggested that AKT pathway alteration was a potential PFS treatment effect modifier. However, the predictive effect of AKT pathway alterations was considered uncertain by the commentary because*:*

- The PFS benefit remained equivocal in the known non AKT pathway altered and unknown AKT status subgroups as these were conducted *post hoc*, were not adjusted for multiplicity, and characteristics for these subgroups were not presented in the submission. *The pre-MSAC response maintained that because baseline characteristics were balanced across the subgroups in both treatment arms in the Capitello study, this supported the robustness of the post hoc analysis.*

- CAPItello-291 and FAKTION did not use the proposed test, Roche AVENIO CGP, to detect AKT pathway alterations and the concordance analysis against FoundationOneCDx was uncertain.

- Placebo + FULV is not the only 2L SOC and may not be representative of 2L treatments. Therefore, the comparative treatment effect of CAPI+FULV compared to placebo + FULV may not be applicable to inform the predictive significance of AKT pathway alteration status treated with current 2L+ SOC.

The commentary noted that results from CAPItello-291 and tests for interaction conducted during the evaluation suggested AKT pathway alteration was predictive of a PFS benefit when compared to patients with known non AKT pathway alterations (excluding all patients with an unknown AKT alteration test result). This was not observed when compared to all patients who did not have a positive AKT pathway alteration test result. In clinical practice, the complement to the requested population of patients with positive AKT alteration test results would be any patient without a positive AKT alteration test result, which by definition would include all patients with an unknown result. However, the lack of a treatment effect modification in this comparison could be related to the performance of FoundationOneCDx as the clinical utility standard (15% of all patients were classified as having unknown AKT pathway alteration in CAPItello-291) as opposed to the predictive validity of the biomarker. *The ESCs noted that the lack of predictive effect might also reflect the limitations of testing on archival tissue potentially collected prior to progression on endocrine therapy. The pre-MSAC response argued in Australia, the rigorous standards for biopsy handling and analysis are expected to result in lower rates of pre-analytical failures, ensuring more accurate and reliable testing results.*

The ESCs noted that AKT pathway alterations, particularly PIK3CA mutations, could be acquired over time. Therefore, a proportion of patients identified as known non AKT pathway status in CAPItello-291 might have harboured an acquired mutation (i.e. were false negatives). Although the submission noted that fresh tissue samples were preferred for testing, this was not a requirement in the trial or in the proposed item descriptor. The pre-MSAC response noted advice from Australian pathologists suggest that it is uncommon for patients to acquire additional AKT pathway alterations following the diagnosis of metastatic diseases.

The submission considered that AKT pathway testing was not expected to introduce additional safety concerns for patients. The commentary noted that testing was permitted once per primary tumour diagnosis under the proposed MBS item descriptor. However, there remained a possibility of re-testing for test failures or false test results, and it might not be reasonable to claim that there would be no additional safety concerns if re-biopsy is required. There would also be a risk that test failures might delay timely access to optimal treatment. *The ESCs considered that testing of fresh tissue (i.e. collected after recurrence or progression on or after endocrine therapy) would be preferable in order to detect any acquired mutations that may be relevant to treatment eligibility.*

Overall, the commentary considered it was likely that CAPI+FULV was more effective than placebo + FULV in AKT pathway altered patients. However, the commentary considered there might not be sufficient evidence to support exclusion of patients without a positive AKT alteration test result (i.e., patients without a positive AKT pathway result) from CAPI+FULV treatment. The PSCR (p1) argued that "identifying AKT pathway alterations through comprehensive genomic profiling using next generation sequencing (NGS) is pivotal in personalising treatment plans for these patients". *The ESCs agreed with the commentary that there remained some uncertainty regarding the rationale behind excluding patients who did not test positive to AKT pathway alteration from treatment with CAPI+FULV. However, the ESCs advised that consideration should also be given to*

the fact that CAPI+FULV has inferior safety compared with FULV monotherapy. Given potential safety concerns, treating patients without AKT pathway alterations, who are less likely to benefit from CAPI+FULV, may not be clinically appropriate.

12. Economic evaluation

The submission presented a modelled economic evaluation, based on the direct randomised trial, CAPItello-291, comparing the proposed test scenario (NGS tumour tissue testing for the detection of AKT pathway alterations [*PIK3CA, AKT1*, or *PTEN*]) with the comparator test scenario (no testing) in patients with HR+/HER2- locally advanced or metastatic breast cancer who progressed on or after an ET with or without a CDK4/6 inhibitor.

Table 13 presents the summary of the economic model components.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Comparison modelled	<u>Proposed test scenario</u>: NGS tumour tissue testing for AKT pathway alterations (*PIK3CA, AKT1,* or *PTEN*). AKT pathway altered patients are treated with CAPI+FULV, non AKT pathway altered patients and unknown AKT status patients are treated with placebo + FULV <u>Comparator test scenario</u>: No testing. All patients treated with placebo + FULV.
Time horizon	15 years in the model; median follow up was 14.9 months (CAPI+FULV arm) and 14.3 months (PBO+FULV arm) in CAPItello-291
Outcomes	PFS years gained, LYG, QALYs gained
Methods used to generate results	Partitioned survival model
Health states	PF, PD, Death
Cycle length	28-day cycle-length
Test parameters	Based on assumptions: Prevalence = 50% Sensitivity = 99% Specificity = 99% Test failure rate = 5% Test uptake rate = **redacted**%
Implications of false positive and false negative results	<u>False positive patients</u>: treated with and incur costs associated with CAPI+FULV but are assumed to experience PFS and OS of placebo + FULV arm in the ITT cohort from CAPItello-291. <u>False negative and Test failure patients</u>: treated with and incur costs associated with placebo + FULV but are assumed to experience PFS and OS of placebo + FULV arm in the ITT cohort from CAPItello-291
Transition probabilities or Allocation to health states (if partitioned survival model)	The allocation of patients to the branches in the proposed and comparator test scenarios were informed by the test parameters. CAPItello-291 was used to inform the PFS and OS curves. The proportion allocated to each branch and data sources informing PFS and OS curves are shown in the table below. <table><tr><td>Branch</td><td>% allocation</td><td>Data source informing PFS and OS</td></tr><tr><td colspan="3">Proposed test scenario</td></tr><tr><td>P1: True positives (Altered)</td><td>44.7%</td><td>CAPI+FULV arm from the Altered subgroup</td></tr><tr><td>P2: False negatives (Altered)</td><td>0.45%</td><td>PBO+FULV arm from the Altered subgroup</td></tr><tr><td>P3: False positives (non-Altered)</td><td>0.45%</td><td>PBO+FULV arm from the ITT cohort</td></tr><tr><td>P4: True negatives (non-Altered)</td><td>44.7%</td><td>PBO+FULV arm from the ITT cohort</td></tr><tr><td>P5: Test failure (Altered)</td><td>4.9%</td><td>PBO+FULV arm from the ITT cohort</td></tr><tr><td>P6: Test failure (non-Altered)</td><td>4.9%</td><td>PBO+FULV arm from the ITT cohort</td></tr><tr><td colspan="3">Comparator test scenario</td></tr><tr><td>C1: Not tested (Altered)</td><td>50%</td><td>PBO+FULV arm from the ITT cohort</td></tr><tr><td>C2: Not tested (non-Altered)</td><td>50%</td><td>PBO+FULV arm from the ITT cohort</td></tr></table>

Component	Summary
	Source: constructed during the evaluation from Section 3.2.2 of the submission; Table 3.5, p190 of the submission *The model was not sensitive to the changes in the cost and outcomes in branches representing the false negatives (P2), false positives (P3), or test failures (P5 and P6) since these contributed to <5% of the total model cohort.*
Extrapolation method	KM data used until only 20% of patients remained at risk then parametric distributions applied to extrapolate to 15 years. Base case extrapolations are shown in the table below.

Branch	Data source	Parametric distribution		
		PFS	OS	TTD
-	Point of truncation	11 months	19 months	12 months
P1	CAPI+FULV (Altered)	Log normal	Log normal	Log normal
P2	Placebo + FULV (Altered)	Log normal	Exponential	NA
P3-P6; C1-C2	Placebo + FULV (ITT)	Log normal	Exponential	NA

Source: Section 3.4.2 and 3.4.3 of the submission

In the test scenario (branches P1-P6), 71% of QALYs gained and 34% of total costs occur in the extrapolated period. In the no test scenario (branches C1-C2), 68% of QALYs gained and 39% of total costs occur in the extrapolated period.

| Component	Summary
Health related quality of life	PF = 0.784. Based on EQ-5D-5L data from CAPItello-291 transformed using algorithm by Viney 2011. PD = 0.623. Based on the average of PD utility values from CAPitello-291 (transformed using Viney 2011) and external sources (Lloyd 2006, previous PBAC considerations including: Olaparib PSD March 2023/November 2023, Olaparib PSD July 2024, Atezolizumab PSD March 2021, Pembrolizumab PSD March 2023, Trastuzumab PSD July 2022, and Sacituzumab govitecan PSD July 2023) AE disutilities included diarrhoea, rash maculopapular, rash, hyperglycaemia, hypokalaemia. AE rates were from CAPItello-291, and disutility values informed by Nafees 2008, Evans 2023, and Huxley 2017. Disutilities associated false positive or false negative test results were not considered by the submission.
Healthcare resource use and costs	The submission included the following: - Testing costs (proposed fee $2,200 per test) - CAPI costs (Treatment duration informed by TTD curves from CAPItello-291) - FULV costs (Treatment duration from CAPItello-291) - Disease monitoring costs (PF and PD health states; clinical expert opinion) - Subsequent anti-cancer therapies (CAPItello-291) - Radiotherapy (clinical expert opinion) - Terminal care costs (informed by Reeve 2018 and T-DXd PSD July 2022) - AE management costs on CAPI or FULV (AE frequency in CAPItello-291) and AE management costs post-progression (AE frequency of chemotherapy in OlympiAD trial)[a]

Source: Section 3.2, 3.4, 3.5 of the submission

AE = adverse event; AKT = serine/threonine kinase; CAPI = capivasertib; DCO1 = data cutoff 1; EQ-5D = Euro-QoL 5 dimension; FULV = fulvestrant; ICER = incremental cost effectiveness ratio; ITT = intention to treat; KM = Kaplan Meier; LYG = life year gained; NA = not applicable; OS = overall survival; PBO = placebo; PD = progressed disease; PF = progression free; PFS = progression free survival; PSD = Public Summary Document; PSM = partitioned survival model; QALY = quality adjusted life years; T-DXd = trastuzumab deruxtecan; TTD = time to treatment discontinuation

[a] OlympiAD trial was a randomised controlled trial that compared olaparib with standard therapy in patients with a germline *BRCA* mutation and hormone receptor-positive/human epidermal growth factor receptor type 2-negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease.

The structure of the economic model is shown in Figure 1.

Figure 1: Model structure
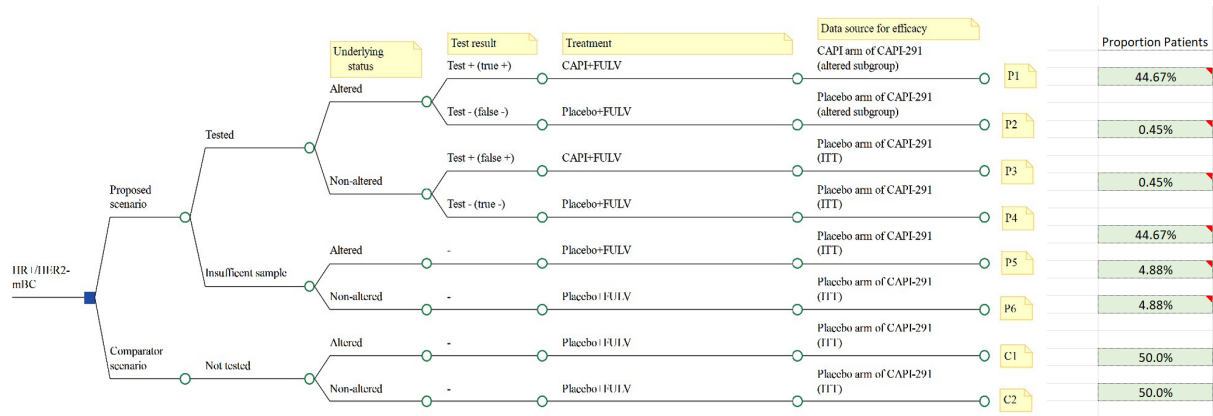
Source: 'Model Outline' worksheet from the economic model
CAPI = capivasertib; FULV = fulvestrant; HR+ = hormone receptor positive; HER2- = Human epidermal growth factor receptor 2 negative; ITT = intention to treat

The submission (p178) assumed that patients eligible for AKT pathway testing enter the model and testing occurs at or soon after diagnosis of HR+/HER2- locally advanced or metastatic disease, or at disease progression to metastatic disease setting. Under the proposed test scenario, patients undergo AKT pathway testing and will either receive a test result or the test fails (due to insufficient sample). Positive patients are treated with CAPI+FULV; negative patients are treated with placebo + FULV; and test failure patients are treated with placebo + FULV. Under the comparator scenario, patients do not undergo testing and all patients are treated with placebo + FULV.

The commentary considered the comparison between the proposed test scenario and comparator test scenario was appropriate for the claims made in the submission. However, the commentary noted there was uncertainty in unequivocally excluding the complement subgroup (non-positive AKT pathway altered patients) from treatment with CAPI+FULV. A scenario analysis was performed during the evaluation, that assumed no AKT pathway testing and the non-biomarker selected population were treated with CAPI+FULV (this was not conducted in the submission). This scenario analysis led to a **redacted**% increase in the incremental cost effectiveness ratio (ICER).

The commentary considered the data sources informing the test branches were broadly reasonable; however, assuming that non-positive AKT pathway altered patients and patients who do not test would elect treatment with placebo + FULV may not be representative of clinical practice. The commentary acknowledged that the comparator in CAPItello-291 was placebo + FULV; however, in clinical practice, patients may elect for other therapies since FULV monotherapy is not the established SOC in the 1L or 2L setting and beyond (e.g., ET+CDK4/6 inhibitor, EVE+EXE, T-DXd, olaparib). The incremental benefit is considered potentially overestimated compared to clinical practice by the commentary.

Furthermore, the submission inconsistently defined the test setting as being in the 1L only (page 217), 1L and 2L (page 186), or in all lines of the advanced or metastatic setting (p178). This created confusion as to the time at which patients are intended to undergo testing and treatment with CAPI+FULV. The MBS item descriptor required patients to have progressed on an ET prior to being eligible for testing and would technically allow patients to be tested at any stage of the advanced or metastatic setting (the MBS item descriptor as it stands would also allow *de novo* patients, but this requires clarification from the sponsor). Based on the distribution in CAPItello-291, which was the basis for most of the efficacy inputs in the model, this may suggest that patients were predominantly treated in the 2L setting (~62-64%), although ~21% of patients were tested and treated in the 3L and ~4% in the 4L setting. Nonetheless, the treatment line at which patients are intended to be tested and treated was not made clear in the submission, and this added uncertainty to the applicability of incremental costs and benefits from the model to clinical practice (e.g., the comparative benefit may vary across treatment lines).

The test parameters that informed the proportion of patients within each branch were all based on assumptions that were considered highly uncertain and potentially optimistic by the commentary. In particular:

- The diagnostic accuracy was assumed to be similar to *BRCA* tumour testing; however, PASC has previously considered the diagnostic accuracy evidence supporting the Roche AVENIO CGP to be uncertain; the Roche AVENIO CGP is not TGA approved; and the NGS assay intended for use in clinical practice and its diagnostic accuracy remains unclear.

- The test failure rate was assumed to be 5% despite 15% of patients in CAPItello-291 having an unknown AKT pathway alteration result.

However, the model was not sensitive to changes in test parameters (**redacted**% change in the ICER, with the largest impact being a reduction of sensitivity/specificity from 99% to 90% leading to a **redacted**% increase).

The proposed fee for testing was $2,200 per test. The commentary noted this is considerably more expensive compared to the proposed cost for NGS testing for *PIK3CA* alterations as well as testing based on ctDNA samples (indicative cost = $350 to $400 per test). The submission cited MBS item 73296 for *BRCA* mutation testing with a fee of $1,200. Applying a test cost of $350 led to a **redacted**% decrease in the ICER and a test cost of $1,200 led to a **redacted**% decrease in the ICER.

The commentary considered the testing costs were potentially underestimated. The submission did not consider re-testing costs for patients with an unknown test result or false test result, or the associated cost of biopsy or re-biopsy. Since the submission assumed a lower test failure rate than CAPItello-291 (15%), these costs are further underestimated. For patients who initially test negative but are eligible for a second test post-progression the associated re-testing/re-biopsy costs were also not considered by the submission. However, the commentary acknowledged that testing under the MBS item descriptor is once per primary tumour diagnosis, so secondary testing may present as an out-of-pocket expense for these patients.

The undiscounted CAPI cost per treatment course in true positive patients (branch P1) was $**redacted** (discounted cost was $**redacted**) and was estimated from the time to treatment discontinuation (TTD) curve from CAPI+FULV (Altered) data extrapolated using the log normal function. Treatment duration was 10.6 months (including adjustment for 0.14 months of dose interruption). This was considered reasonable by the commentary.

The CAPI costs per treatment course in false positives (branch P3) was $**redacted** and was estimated by multiplying the cost per cycle of CAPI ($**redacted**) by the median PFS (3.7 months) of the non AKT pathway altered subgroup who received placebo + FULV in CAPItello-291. This was considered a crude assumption by the commentary; however, it is acknowledged that data to inform the treatment duration of false positive patients was not available. An alternative method of using the PFS curve as a proxy for the TTD curve in false positive patients was tested during the evaluation. This increased the cost of CAPI to $**redacted** over a 15-year time horizon; however, due to the small number of false positive patients assumed in the base case (0.45% of all patients) this had a very small impact (**redacted**%) on the ICER.

The submission inappropriately applied an 86.2% relative dose intensity (RDI) to CAPI costs based on the AKT pathway altered subgroup from CAPItello-291; since the proposed price for the 200 mg and 160 mg tablets were identical, patients who have a dose reduction will be incurring the same cost for CAPI treatment. This underestimated CAPI costs and removing the RDI led to a **redacted**% increase in the ICER. The model was not sensitive to changes in AE management costs, disease monitoring costs, post-progression costs, and terminal care costs.

The key drivers of the model were the OS extrapolations of the CAPI+FULV (Altered) branch P1 and of the placebo + FULV (ITT) branches P3-C2, and the time horizon. Modelling of OS was considered optimistic by the commentary and favoured the CAPI+FULV branch over the placebo + FULV branches. The base case time horizon of 15-years was longer than time horizons previously considered by the PBAC in the same population (a 10-year time horizon was considered but a 7-

year time horizon was accepted in the PBAC's consideration of Ribociclib July 2020/November 2020 in 2L HR+/HER2- locally advanced or metastatic breast cancer). The base case PFS and OS extrapolations from the model are presented in Figure 2.

Figure 2: Base case PFS and OS curves
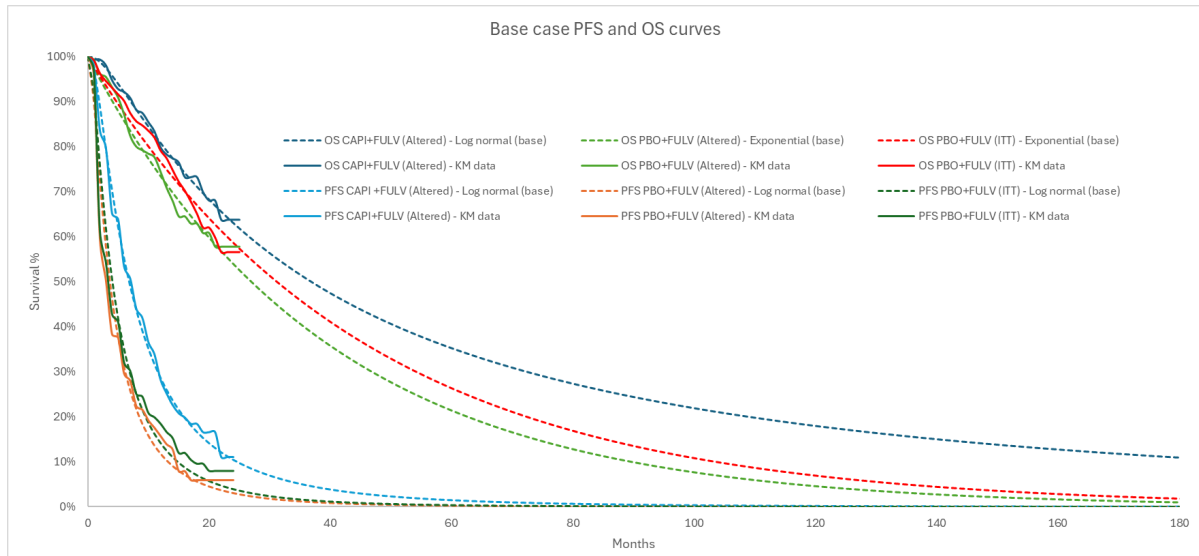
Source: constructed during the evaluation using 'PFS KM data', 'OS KM data', 'Extrapolations CAPI (P1)', 'Extrapolations placebo (P2)', and 'Extrapolations placebo (ITT)' worksheets from the economic model
CAPI = capivasertib; FULV = fulvestrant; KM = Kaplan Meier; PBO = placebo; PFS = progression free survival; OS = overall survival

The model included utility values for the progression free (PF) health state, progressed disease (PD) health state, and disutility for AEs experienced from CAPI+FULV. However, the submission did not consider disutility associated with patients who receive a false positive or false negative result from AKT pathway testing. Although this was not expected to have a large impact the ICER since the proportion of patients in these branches (P2 and P3) was <1%. The derivation of the PD health state utility value in the submission's base case was not reasonable and the PD utility from CAPItello-291 (0.748) was considered as the more generalisable source. The utilities had a moderate impact on the ICER.

The disaggregated costs and outcomes by branch are presented in Table 14.

Table 15: Disaggregated costs and outcomes (discounted)

Costs	Testing						No testing			Inc (Test vs no test)	% of total Inc
	Total	P1 (TP)	P2 (FN)	P3 (FP)	P4 (TN)	P5-P6 (TF) a	Total	C1	C2		
% per branch	-	44.7%	0.45%	0.45%	44.7%	4.9%	-	50%	50%	-	-
Capivasertib and placebo	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	redacted%
Fulvestrant	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	redacted%
Subsequent anti-cancer therapies	$11,229	$4,352	$56	$56	$5,553	$1,212	$12,430	$6,215	$6,215	-$1,200	-4.8%
Surgery/radio therapy post recurrence	$267	$119	$1	$1	$120	$26	$269	$134	$134	-$1	0.0%
Adverse events management	$84	$80	$0	$0	$3	$1	$7	$3	$3	$78	0.3%
Adverse events from subsequent treatments	$344	$152	$2	$2	$154	$34	$345	$173	$173	-$2	0.0%
Disease monitoring	$15,000	$7,777	$53	$59	$5,837	$1,274	$13,065	$6,532	$6,532	$1,935	7.7%
Terminal care	$22,679	$9,568	$109	$107	$10,585	$2,310	$23,695	$11,847	$11,847	-$1,015	-4%
Testing costs	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	redacted%
Total	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted	redacted%
LYG											
PF	0.67	redacted	redacted	redacted	redacted	redacted	0.52	redacted	redacted	0.15	redacted%
PD	2.67	redacted	redacted	redacted	redacted	redacted	2.39	redacted	redacted	0.28	redacted%
Total LYG	**3.34**	redacted	redacted	redacted	redacted	redacted	**2.91**	redacted	redacted	**0.43**	redacted%
QALY gained											
PF	0.53	redacted	redacted	redacted	redacted	redacted	0.41	redacted	redacted	0.12	redacted%
PD	1.66	redacted	redacted	redacted	redacted	redacted	1.49	redacted	redacted	0.18	redacted%
Total QALY gained	**2.19**	redacted	redacted	redacted	redacted	redacted	**1.90**	redacted	redacted	**0.29**	redacted%

Source: Constructed during the evaluation using 'ICER'; 'model outline'; 'Trace – CAPI (P1)'; 'Trace – placebo (P2)'; and 'Trace – placebo (ITT)' worksheets from the economic model

FN = false negative; FP = false positive; LYG = life year gained; PD = progressed disease PF = progression free; QALYs = quality adjusted life years; TP = true positive; TN = true negative; TF = test failure

a Branches P5, and P6 were treated identically (same costs and outcomes)

b Cost of test failures that incur an MBS fee ($18.81)

Note: the costs and outcomes in each branch were weighted by the proportion of patients in each branch

The estimated test cost per patient was $redacted. As noted earlier, the test parameters were considered uncertain by the commentary as they were based on assumptions that were possibly optimistic; testing costs were potentially underestimated as potential out-of-pocket costs associated with re-testing (and re-biopsy) in patients with an unknown test result were not considered; and subsequent testing for patients who initially test negative but develop an AKT pathway alteration upon disease progression was also not considered.

The base case ICER was $75,000 to <$95,000 per QALY gained. The ICER was primarily driven by the higher incremental cost of CAPI in the proposed test scenario compared to the comparator scenario ($**redacted**, ~**redacted**% of total incremental costs), and the greater time spent in the PD health state by the proposed test scenario compared to the comparator scenario (0.28 incremental LYG, ~66% total incremental LYG). Costs and outcomes in the test scenario were predominantly incurred in branches P1 (true positive) and P4 (true negative), as the model assumed that the majority of patients occupied these branches. Testing costs only contributed to **redacted**% of total incremental costs; however, as noted above, testing costs were potentially underestimated.

Sensitivity analyses

The results of key univariate and multivariate sensitivity analyses are summarised in Table \15.

Table 16: Sensitivity analyses conducted by the submission and additional analyses during the evaluation

		Inc QALY	Inc cost	ICER ($/QALY gained)	%Δ
-	**Base case**	**redacted**	**$redacted**	**$redacted** [1]	**-**
Test parameters					
-	Prevalence of AKT alteration 40% (base case 50%)	redacted	$redacted	$redacted [1]	redacted
-	Prevalence of AKT alteration 60% (base case 50%)	redacted	$redacted	$redacted [1]	redacted
-	Test accuracy 100% (base case 99%)	redacted	$redacted	$redacted [1]	redacted
-	Test accuracy 95% (base case 99%)	redacted	$redacted	$redacted [1]	redacted
	Test failure rate 15% (base case 5%)	redacted	$redacted	$redacted [1]	redacted
Univariate sensitivity analyses conducted during the evaluation					
Testing parameters: test costs (base case $2,200) or test accuracy (base case 99%)					
#1	Test cost $350	redacted	$redacted	$redacted [1]	redacted
#2	Test cost $1200	redacted	$redacted	$redacted [1]	redacted
#3	Test accuracy 90%	redacted	$redacted	$redacted [1]	redacted

Source: constructed during the evaluation using Table 3.40, pp232-3 of the submission and the economic model
ICER = incremental cost effectiveness ratio; Inc = incremental; QALY = quality adjusted life year; %Δ = percentage change from the submission's base case ICER
Univariate sensitivity:
#1: set Cell B19 = $350 in 'Resource use' worksheet
#2: set Cell B19 = $1,200 in 'Resource use' worksheet
#3: set Cells B15 and B16 = 90% in 'Assumptions' worksheet
Italicised text indicates additional sensitivity analyses conducted during the evaluation

The redacted values correspond to the following ranges:
[1] $75,000 to <$95,000

Scenario analysis – non-biomarker selected population

Given the uncertainty in excluding the complement subgroup (i.e., non-positive AKT pathway altered patients) from treatment with CAPI+FULV, a scenario analysis was conducted during the evaluation that assumed no testing and that CAPI+FULV is available to all patients irrespective of biomarker status. This is of relevance because the TGA indication for the treatment is not biomarker-specific, and this analysis was also requested by PASC (p25, 1766 Ratified PICO Confirmation, April 2024 PASC Meeting).

The scenario analysis also assumed that all data were informed by the ITT cohort for CAPI+FULV and placebo + FULV arms, respectively. The placebo + FULV ITT extrapolations and inputs remained unchanged from the base case settings (i.e., extrapolated PFS using log normal and OS using exponential). Using the parametric distributions with the best AIC/BIC statistics and upholding visual plausibility, the generalised gamma and log logistic were selected to extrapolate PFS and OS in the CAPI+FULV ITT arm, respectively. The results are shown in Table 16.

Table 17: Scenario analysis results – non-biomarker population

		Inc LYG	Inc QALY	Inc cost	ICER	% Δ
-	**Base case (biomarker selected)**	**0.43**	**0.29**	$redacted	$redacted [1]	**-**
E1	**CAPI + FULV (ITT) PFS = gen gamma; OS = log logistic**	**0.67**	**0.48**	$redacted	$redacted [2]	redacted
E2	CAPI + FULV (ITT) PFS = log normal	0.67	0.45	$redacted	$redacted [2]	redacted
E3	CAPI + FULV (ITT) OS = exponential	0.32	0.26	$redacted	$redacted [4]	redacted
E4	E1 + time horizon 10 years	0.48	0.36	$redacted	$redacted [3]	redacted
E5	E4 + RDI 100%	0.48	0.36	$redacted	$redacted [4]	redacted
E6	E5 + trial-based PD utility 0.748	0.48	0.38	$redacted	$redacted [4]	redacted

Source: constructed during the evaluation using the economic model and Attachment 3.2 to the submission
AIC = Akaike information criterion; BIC = AIC = Bayesian information criterion; CAPI = capivasertib; FULV = fulvestrant; Inc = incremental; ICER = incremental cost effectiveness ratio; LYG = life year gained; PBO = placebo; QALYs = quality adjusted life years; %Δ = percentage change from the submission's base case ICER
E1: assumed no testing (including associated testing costs); efficacy was informed by CAPI+FULV arm from ITT data (including extrapolations); extrapolations selected according to best AIC/BIC fit (PFS = gen gamma and OS = log logistic)
E2: same as E1 except PFS extrapolation = log normal
E3: same as E1 except OS extrapolation = exponential (despite being the last ranked AIC/BIC fit, this extrapolation produced an OS curve with convergence and did not cross over with the placebo + FULV base case extrapolations).
E4: same as E1 and additionally set the time horizon to 10 years
E5: same as E4 and additionally set RDI = 100% (Cell B12 = 100%, 'Drug costs' worksheet)
E6: same as E5 and additionally applied the trial-based PD utility value (Cell B6 = 0.748, 'Utilities' worksheet)

The redacted values correspond to the following ranges:
[1] $75,000 to <$95,000
[2] $95,000 to <$115,000
[3] $135,000 to <$155,000
[4] $155,000 to <$255,000

Assuming no testing and that patients are treated irrespective of biomarker status, and applying the best statistically fitting curves, led to a **redacted**% increase in the base case ICER (from $75,000 to <$95,000/QALY to $95,000 to <$115,000/QALY gained; scenario E1). Under this scenario CAPI is now received in 100% of the 'intervention arm' rather than only ~45% in the proposed test scenario base case and the ITT results showed a benefit in all patients treated with CAPI+FULV (0.93 LYG in the scenario vs 0.67 LYG in the base case). This increased the cost of CAPI treatment in the scenario analysis compared to the base case ($**redacted** vs $**redacted**) and was accompanied by a greater QALY gain (0.48 vs 0.29 incremental QALY gain); albeit to a lesser extent compared to the cost increase. Testing costs were no longer incurred, though this accounted for only **redacted**% of the total incremental cost in the submission's economic evaluation.

Assuming scenario analysis E1 as representative of treating non-biomarker selected patients, the resulting modelled PFS and OS curves are presented in Figure 4. Additionally applying a time horizon of 10 years, an RDI of 100%, and the trial-based PD utility value (0.748) led to a net **redacted**% increase from the base case ICER ($155,000 to <$255,000 per QALY gained i.e., scenario analysis B6).

Figure 3: Modelled PFS and OS in scenario E1
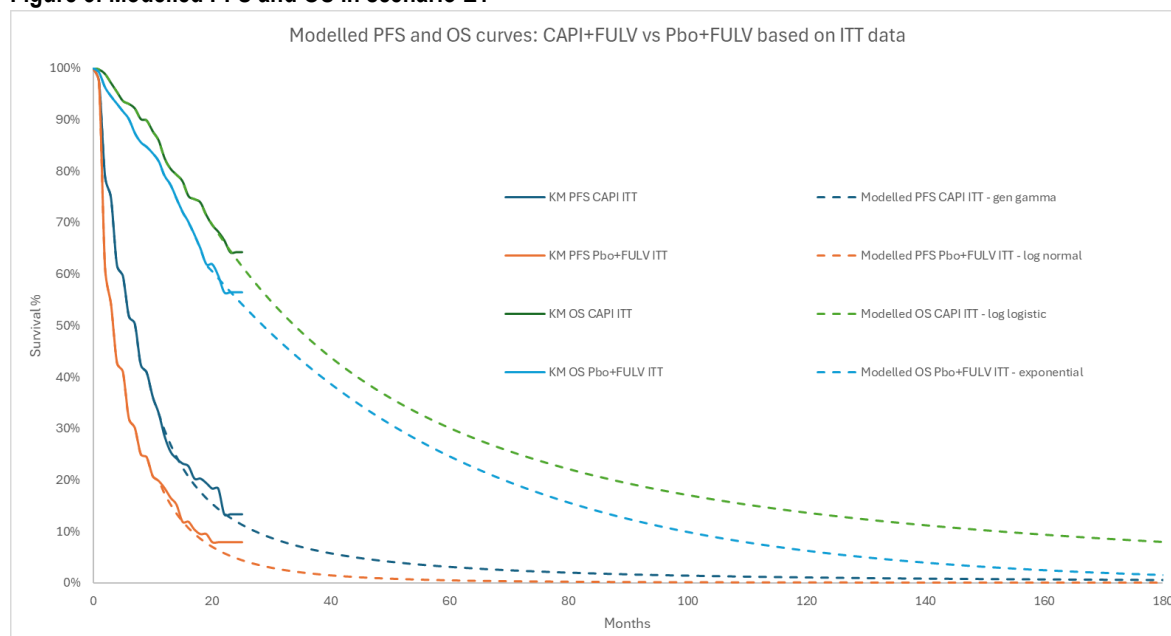
Source: constructed during the evaluation using 'Extrapolations CAPI (P1)' and 'Extrapolations CAPI ITT' worksheets from the economic model and Attachment 3.2 to the submission
CAPI = capivasertib; FULV = fulvestrant; ITT = intention to treat; PFS = progression free survival; OS = overall survival
Note: extrapolation selected base on best statistical AIC/BIC fit and visual plausibility

13. Financial/budgetary impacts

The submission adopted an epidemiological approach to estimate the financial impact of testing for AKT pathway alterations (*PIK3CA, AKT1,* or *PTEN*) and treatment with CAPI+FULV in patients with HR+/HER2- locally advanced or metastatic breast cancer following disease progression or recurrence on or after an ET with or without a CDK4/6 inhibitor.

The inputs and data sources used are presented in Table 17.

Table 18: Key inputs for financial estimates

Data	Value and source	Comment
Eligible population		
BC incidence	The submission obtained the BC incidences from the AIHW Cancer in Australia 2021 report (Table S3.4 'Cancer in Australia Chapter 3 – Cancer projections and Australia's ageing population' data table).	Reasonable
% Stage III-IV BC	The submission estimated the proportion of Stage I-IV BC (including unknown) based on the AIHW Australian Cancer Database 2014. The submission calculated the proportion of advanced or metastatic BC with an adjustment for unknown patients (17.68%)	Reasonable. The approach for adjusting for unknown patients was also accepted by the PBAC and DUSC for Olaparib (Table 20, Olaparib PSD, March 2023 PBAC Meeting)
% HR+/HER2- subtype	The proportion of HR+/HER2- subtype was 70%. The submission stated that this proportion was accepted by the PBAC in its consideration of Sacituzumab govitecan in July 2023.	Reasonable. This was noted to be consistent with previous submissions to the PBAC (fulvestrant PSD, July 2020 PBAC Meeting; and abemaciclib PSD, March 2022 PBAC Meeting).
Test uptake rate	The submission assumed a gradual uptake rate of **redacted**% in Year 1 **redacted**% in Year 6. The submission assumed uptake rate would be similar to BRCA testing that was used in the submission for Olaparib in November 2023.	Test uptake rate in Year 1 and 2 may be underestimated considering that testing in breast cancer patients is common practice.

Data	Value and source	Comment
% HR+/HER2- locally advanced or metastatic on 1L CDK4/6i	The submission based the number of HR+/HER2- locally advanced or metastatic BC patients treated in the 1L with a CDK4/6i on DUSC estimates of CDK4/6i use. The submission stated that DUSC applied a 2% annual growth rate. The submission (p238) stated this estimation was based on Sacituzumab govitecan PSD July 2023 and Trastuzumab deruxtecan November PSD November 2023. The submission assumed that the proportion of patients who did not receive a CDK4/6i in the 1L could be eligible for CAPI+FULV in the 1L setting.	Sourcing 1L CDK4/6i use from the DUSC was reasonable, however, the 2025 to 2030 estimates could not be verified or reproduced during the evaluation. The Sponsor is requested to explain how these numbers were derived.
% Patients who progress from 1L to 2L treatment	The proportion of patients who progress from 1L to 2L setting = 88%. The submission stated this was based on the KARMA registry (Wong 2022). KARMA was established in August 2019 as a study of Australian patients who received 1L combination treatment of ribociclib and an AI, where ribociclib was obtained through a medicines accept program between May 2017 and June 2018, This access program included postmenopausal women with HR+/HER2- metastatic BC who had not received prior systemic treatment in the metastatic setting. Wong 2022 (N=160) reported that of the 74 patients who had disease progression on 1L ribociclib + AI, 65 patients (88%) received a 2L therapy. The mean age of patients in the registry was 54.3 years.	Reasonable. The submission assumed that of the patients on 1L CDK4/6i, 88% will progress and be eligible for CAPI in the 2L. The requested restriction allows for testing and treatment any time after disease progression on or after an ET. As such, patients in the 3L+ setting would also be eligible for testing and CAPI+FULV. Omission of patients from the 3L+ who have not had CDK4/6i may potentially underestimate the financial estimates.
Utilisation		
MBS items	The proposed MBS fee for AKT pathway testing was $2,200 per test. The submission applied the 85% MBS rebate ($1,870).	Acknowledging the MBS item descriptor allows one test per primary tumour diagnosis, it was not clear how patients with an unknown test result would be handled in practice or if retesting could occur in patients who initially test negative but develop an alteration after disease progression. It is possible these scenarios could lead to out-of-pocket cost to patients and present a potential equity issue and whether these patients would subsequently be eligible for CAPI + FULV if the second test was positive. The submission did not apply the Greatest Permissible Gap ($98.70) to the MBS rebate. This underestimated the MBS costs. The MBS fee applying the Greatest Permissible Gap was $2,101.3.
Cost offsets	A cost offset was calculated assuming that 10% of patients will receive AKT pathway testing from Year 1 to Year 6 in absence of an MBS-funded test.	The basis for claiming that 10% of patients would already know their AKT pathway alteration status was unclear. The estimation of number of tests in 2L patients (after CDK4/6i) was overestimated as the submission did not consider that only the 88% of patients who progress from 1L to 2L would be tested.

Source: constructed using information from Section 4.1 to 4.3 of the submission

AI = aromatase inhibitor; AIHW = Australian Institute of Health and Welfare; AEMP = approved ex-manufacturer's price; ARTG = Australian Register of Therapeutic Goods; BC= breast cancer; CAPI = capivasertib; CDK4/6i = Cyclin-dependent kinases 4 and 6 inhibitor; CGP = comprehensive genomic profiling; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = endocrine therapy; FULV = fulvestrant; HR+ = hormone positive; HER2- = Human epidermal growth factor receptor 2 negative; KARMA = Kisqali Access Registry for Metastatic breast cancer in Australia; NGS = Next Generation Sequencing; PASC = PICO Advisory Sub-Committee; para = paragraph; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; pts = patients; SOC = standard of care; RPBS = Repatriation Pharmaceutical Benefits Scheme; 1L = first line; 2L = second line

The patients eligible for testing and the net cost to the MBS is presented in Table 18.

The commentary noted the submission was inconsistent with its calculation of total tested patients, because there was no adjustment for the fact that only the 88% of patients who progress from 1L to 2L prior will be eligible for testing for treatment in the 2L setting. Table 18 presents the estimated tested population that incorporated the 88% of patients who progress from 1L to 2L (E1 and E4); as well as what was presented in the submission and financial workbook (E2 and E3).

Table 19: Estimated use and financial implications

		Value	2025	2026	2027	2028	2029	2030
A1	BC incidence	-	22,221	22,709	23,186	23,678	24,173	24,667
A2	Stage III/IV BC (17.7%)	A1×17.7%	3,928	4,015	4,099	4,186	4,273	4,361
A3	HR+/HER2- subtype (70%)	A2×70%	2,750	2,810	2,869	2,930	2,991	3,053
Pts eligible for 1L testing								
B1	Pts on 1L CDK4/6i	DUSC estimates	redacted [2]	redacted [2]	redacted [2]	redacted [2]	redacted [2]	redacted [2]
B2	Pt not eligible for 1L CDK4/6i	A3–B1	redacted [2]	redacted [2]	redacted [1]	redacted [1]	redacted [1]	redacted [1]
B3	**Test uptake rate (1L tested population)**	**B2× redacted[a]**	redacted [1]	redacted [1]	redacted [1]	redacted [1]	redacted [1]	redacted [1]
B4	Pts assumed to have been tested already	B2x10%	redacted [1]	redacted [1]	redacted [1]	redacted [1]	redacted [1]	redacted [1]
Pts eligible for 2L testing (incorporates 88% of patients who progress from 1L to 2L)								
C1	Pts who progress from 1L to 2L after CDK4/6i (88%)	B1×88%	redacted [2]	redacted [2]	redacted [2]	redacted [2]	redacted [2]	redacted [2]
C2	**Test uptake rate (2L tested population)**	**C1× redacted[a]**	redacted [2]	redacted [2]	redacted [2]	redacted [2]	redacted [2]	redacted [2]
C3	Pts assumed to have been tested already	C1x10%	redacted [1]	redacted [1]	redacted [1]	redacted [1]	redacted [1]	redacted [1]
Total tested and treated population								
E1	**Total tested population [b]**	**B3+C2**	redacted	redacted	redacted	redacted	redacted	redacted
E2	Total tested population in submission main body [c]	Tables 4.21 and 4.22 of submission	redacted	redacted	redacted	redacted	redacted	redacted
E3	Total tested population in financial estimate spreadsheet [d]	Sheet 7 of spreadsheet	redacted	redacted	redacted	redacted	redacted	redacted
Net cost MBS (incorporated 88% who progress from 1L to 2L)								
F1	Cost of testing	E1x$1,870[e]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]
F2	Cost offset [f]	(B4+C3) x$1,870	$redacted [4]	$redacted [4]	$redacted [4]	$redacted [4]	$redacted [4]	$redacted [4]
F3	Net cost MBS	F1+F2	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]
Net cost MBS estimated in submission (Assumed patients did not progress from 1L to 2L)								
F4	Cost of testing	E3x$1,870[e]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]
F5	Cost offset [f]	(B4+C3) x$1,870	$redacted [4]	$redacted [4]	$redacted [4]	$redacted [4]	$redacted [4]	$redacted [4]
F6	Net cost MBS	F4+F5	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]	$redacted [3]

Source: constructed from 'Calculation' worksheet of the financial workbook, Table 4.21 and 4.22, p251 of the submission, Sheet 7, financial estimates spreadsheet, Attachment 4.1 to the submission

BC= breast cancer; CDK4/6i = Cyclin-dependent kinases 4 and 6 inhibitor; DUSC = Drug Utilisation Sub Committee; HR+ = hormone positive; HER2- = Human epidermal growth factor receptor 2 negative; pts = patients 2; 1L = first line; 2L = second line

a Test uptake rates: **redacted**

b The total test population presented in E1 are the total tested patients in the 1L and 2L that incorporated the proportion of patients who progressed from 1L to 2L (88%). The submission did not include this proportion in its estimation of the tested population.

c As reported in Tables 4.21 and 4.22 of the submission. Includes offsets from an assumed 10% of patients already knowing AKT pathway alteration status (will not get tested under proposed item)

d As reported in the sheet 7, financial estimates spreadsheet, Attachment 4.1 to the submission. These test numbers correspond to the MBS costs estimated by the submission in Table 4.24, p252 of the submission

e Calculated as the total pts eligible for testing multiplied by $1,870. The submission applied the 85% rebate (testing fee = $1,870) and did not apply the Greatest Permissible Gap ($98.70).

f the cost offset to the MBS assumed that 10% of patients eligible for testing in 1L and 2L (e.g., 10% x 524 = 52 pts in 1L and 10% x 1959 = 196 pts in 2L in Year 1 assumed to have tested already).

Note: the submission assumed that grandfathered patients were not tested again and enter as part of the treated population

The redacted values correspond to the following ranges:

[1] <500

[2] 500 to <5,000

[3] $0 to <$10 million

During the evaluation, an analysis was conducted where the eligible patient population incorporated the 88% of patients who progress from the 1L to 2L setting, the net cost to the MBS was $0 to <$10 million in Year 1 and increasing to $0 to <$10 million in Year 6.

This was lower than the submission's estimates which inappropriately did not include the 88% of patients who progress from the 1L to 2L setting and estimated the net cost to the MBS was $0 to <$10 million in Year 1 increasing to $0 to <$10 million in Year 6.

Table 19 presents the sensitivity analyses of financial estimates as most related to the net cost to the MBS.

Table MSAC.20: Sensitivity analysis conducted during the evaluation (based on effective prices)

	2025	2026	2027	2028	2029	2030	Total	%Δ
The submission's base case net MBS costs								
Cost MBS	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [2]	-
Additional sensitivity analyses conducted during the evaluation								
SA1: Test uptake rate 80% yr1, 85% yr2, 90% yr3, 95% yr4+ (base case: redacted)								
Cost MBS	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [2]	+9%
SA2: Test uptake rate = 95% yr1+ (base case: redacted)								
Cost MBS	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [2]	+15%
SA3: MBS fee = $2,101.3 (base case = $1,870)								
Cost MBS	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [2]	-4%
SA4: Incorporate 88% of patients who progress from 1L to 2L (base case = did not apply)								
Cost MBS	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [2]	-10%
SA5: SA3+SA4								
Cost MBS	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [1]	$redacted [2]	-14%

Source: constructed during the evaluation from pp254-6 of the submission; and the financial workbook
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; SA = sensitivity analysis; tx = treatment; 1L = first line setting; yr = year; %Δ = percentage change from the submission's base case total MBS costs
SA1 = test uptake rate 80% Year 1, 85% Year 2, 90% Year 3, 95% Year 4-6
SA2 = test uptake rate 95% in Year 1-6
SA3 = MBS fee to incorporate Greatest Permissible Gap ($98.70) = $2,101.3.
SA4 = adjust MBS cost offset calculation to incorporate patients who progress from 1L to 2L (88%) and therefore are eligible for testing
SA5: SA3+SA4

The redacted values correspond to the following ranges:
[1] $0 to <$10 million
[2] $20 million to <$30 million

When the 88% of patients who progress from the 1L to 2L setting and the Greatest Permissible Gap ($98.70) were applied in an analysis during the evaluation, the net MBS cost decreased by 14% ($0 to <$10 million in Year 1 increasing to $0 to <$10 million in Year 6).

Overall, the net financial implications were considered uncertain by the commentary, with costs potentially underestimated since:

- The estimates of patients on a 1L CDK4/6 inhibitor that were claimed to be based on the DUSC estimates could not be verified.

- The test uptake rate in the first two years of listing may be higher in practice given that genetic testing in breast cancer is common practice, and the submission excluded patients who could have been potentially tested in the 3L+ setting among patients who have not previously had CDK4/6 inhibitors.

14. Other relevant information

No other significant factors were identified during the evaluation.

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

MBS item descriptor

- The wording of the proposed MBS item descriptor reflected testing earlier in the treatment algorithm than proposed in the PICO confirmation and broader than the population proposed in the PBS restriction, and in the pivotal trial. The broader population is no longer aligned with National Comprehensive Cancer Network (NCCN) guidelines.

Clinical issues

- ESC considered it to be uncertain whether AKT pathway testing should be required prior to treatment with CAPI+FULV, noting:

  - The TGA-approved indication for CAPI+FULV is not limited to patients with an AKT pathway alteration.

  - The pivotal CAPItello-291 trial demonstrated some clinical benefit for all patients regardless of AKT status; however, some patients in the unknown AKT pathway group might have acquired AKT pathway alterations over time without these being detected due to the use of archival tissue.

- Results from CAPItello-291 and tests for interaction suggested that being AKT pathway altered was predictive of a PFS benefit (PFS hazard ratio [HR]=0.50, 95% CI 0.38, 0.65, p<0.001) when compared to patients with known non AKT pathway alterations (excluding unknown AKT pathway status patients; PFS HR=0.79, 95% CI 0.61, 1.02). This was not observed when compared to the non AKT pathway altered subgroup inclusive of patients with unknown AKT pathway status (PFS HR=0.70, 95% CI 0.56, 0.88). The latter subgroup must be considered since the true complement in clinical practice would include both known non AKT pathway altered and unknown AKT status patients. However, it is acknowledged that the lack of a treatment effect modifier in the true complement could be related to the performance of FoundationOneCDx as the clinical utility standard (15% of all patients were classified as having unknown AKT pathway alteration), as opposed to the predictive validity of the biomarker.

- The predictive effect of AKT pathway testing carried some uncertainty as:

  - CAPItello-291 did not use the test proposed for use in Australia (Roche AVENIO) to detect PIK3CA, AKT1, and PTEN variants. Concordance between the Roche AVENIO and the FoundationOneCDx tests was highly uncertain based on the PASC's assessment of the Monash Health Pathology 2024 study. The actual test that will be used in practice was also not clear.

  - The PFS benefit remains equivocal in the known non AKT pathway altered and unknown AKT status subgroups as these were exploratory *post hoc* analyses, were not adjusted for multiplicity, and characteristics for these subgroups were not presented in the submission.

Economic issues

- The ICER was $75,000 to <$95,000/QALY gained and was not sensitive to testing parameters (at most, assuming 90% test accuracy increased the ICER by 7%). A scenario analysis in the non-biomarker selected cohort was conducted during the evaluation using the ITT data from CAPItello-291. This is of relevance because the TGA indication for the treatment is not biomarker-specific, and this analysis was also requested by PASC. This increased the ICER to $$75,000 to <$95,000/QALY gained (**redacted**%).

- The modelled overall survival (OS) in the CAPI+FULV branch and the placebo + FULV (intention-to-treat or ITT) branches and the time horizon were key drivers of the model, with

the difference in OS between CAPI+FULV and placebo + FULV not being significantly different in CAPItello-291.

- The estimated testing cost per patient was $**redacted**, which was poorly justified. However, the test parameters that informed the model were all based on assumptions that were potentially optimistic such as assuming a lower test failure rate (5%) than that reported in the pivotal trial (15%). This assumption was not reasonable given the uncertainties in test performance and test implementation in practice. However, the ICER was not sensitive to testing parameters (at most, assuming 90% test accuracy increased the ICER by **redacted**%).

- The downstream costs of re-testing after disease progression in patients who initially had a non-positive test result were not considered, nor were costs associated with safety concerns (e.g., re-biopsy or delayed time to optimal treatment, or unnecessary adverse events from sub-optimal treatment) which further potentially underestimated testing costs and harms.

Financial issues

- The net costs to the MBS were potentially underestimated given the test uptake rate in the first two years of listing may be higher in practice compared to the submission's base case. This is because genetic testing is commonplace in breast cancer, and patients in the third line and beyond setting were excluded despite being eligible for testing under the MBS item descriptor. The diagnostic accuracy of testing was not incorporated and the prevalence of AKT pathway alterations was uncertain, though the direction of effect was unclear. The net effect was uncertain.

ESCs discussion

The ESCs noted that the integrated codependent submission sought Medicare Benefits Schedule (MBS) listing of Next Generation Sequencing (NGS) testing for the detection of AKT pathway alterations (*PIK3CA, AKT1 or PTEN*) to determine eligibility for treatment with capivasertib in combination with fulvestrant (CAPI+FULV), for patients with hormone receptor positive (HR+)/ human epidermal growth factor receptor 2-negative (HER2-) locally advanced unresectable or metastatic breast cancer following disease progression or recurrence on or after an endocrine-based regimen (i.e. in the second-line [2L]) or later setting), with or without a cyclin dependent kinase 4 and 6 (CDK4/6) inhibitor. The ESCs also noted that the application sought Pharmaceutical Benefits Scheme (PBS) General Schedule Authority Required (Telephone/Online) listing of CAPI+FULV for the treatment of the same population who had evidence of an AKT pathway alteration (*PIK3CA, AKT1* or *PTEN*); however, the ESCs also noted that the TGA indication for CAPI+FULV is not restricted to patients with an AKT pathway alteration.

The ESCs noted and welcomed consultation feedback received from 2 organisations. The ESCs noted that the feedback was supportive of the test being MBS-listed, stating that it would otherwise be unaffordable for patients, and that MBS listing of the test would help to support equity of access to the treatment if it was PBS listed. The ESCs also noted that feedback was supportive of capivasertib listing as a new option for a patient group whose treatment options are currently limited.

The ESCs noted that the proposed MBS item descriptor for testing (Table MSAC. 1) required that patients had locally advanced (inoperable) or metastatic hormone receptor positive (HR+), HER2- breast cancer. The ESCs also noted that, in the pivotal trial CAPItello-291, HR+ status was defined as estrogen-receptor expression (ER+), with or without progesterone-receptor expression (i.e. was more narrowly defined than in the proposed MBS item descriptor). The ESCs noted that HER2- was considered to include HER2-low patients.

The ESCs noted that the test population presented in the applicant-developed assessment report (ADAR) and in the proposed MBS item descriptor differed from the test population considered by PASC, because it was no longer restricted to patients following recurrence or progression on or after aromatase inhibitor (AI) therapy, with or without a CDK4/6 inhibitor as the proposed population had been amended to patients with 'locally advanced (inoperable) or metastatic

hormone receptor positive, HER2- breast cancer OR following recurrence or progression on or after endocrine based regimen, with or without a CDK4/6 inhibitor' where previously it had been 'AND'.[12] The ESCs noted that this resulted in a broader population than in the pivotal CAPItello-291 trial, and the test population that was advised by PASC. In addition, this broader population no longer aligned with National Comprehensive Cancer Network (NCCN) guidelines. The ESCs also noted that this broader population was not in line with the requested PBS item. The ESCs considered that if the MBS item descriptor included 'AND' rather than 'OR', testing of fresh tissue (i.e. collected after recurrence or progression on or after endocrine therapy, in line with the proposed PBS listing) may be more likely, which the ESCs considered would be preferable in order to detect any acquired mutations that may be relevant to treatment eligibility.

The ESCs noted that, in the pre-sub-committee response, the applicant stated that the reason for the population expansion was to ensure that patients whose disease progressed despite receiving endocrine therapy + CDK4/6 inhibitor in the adjuvant setting would not be excluded from access to CAPI+FULV. The ESCs considered that while the proposed expansion might result in expedited treatment for patients tested at an earlier stage, the possibility of false negative results might arise for tumour tests that are performed significantly earlier than the potential treatment initiation time, noting that patients might acquire mutations during the course of the disease. The ESCs noted that endocrine therapy could trigger AKT pathway alterations in breast cancer patients. The ESCs considered that it might be appropriate to restrict the testing population to patients who had received prior treatment with a CDK4/6 inhibitor to ensure consistency with international guidelines and to be in line with a significant proportion of the key trial population. The ESCs also considered whether the proposed broader population might result in unnecessary testing. However, given the high rate of progression in the proposed population, the ESCs considered the risk of unnecessary testing was likely to be small.

The ESCs also noted that the intervention presented in the ADAR and MBS item descriptor had also changed following PASC consideration. The ADAR and MBS item no longer specified that testing was to be performed using NGS, or that it was to characterise tier 1 genetic variants in the relevant AKT pathway genes specifically, but instead only mentioned detection of AKT pathway altered tumour without mentioning the variant tier. The ESCs queried whether the removal of the restriction to tier 1 variants might result in broader use of the test, i.e. in patients with non-pathogenic alterations. However, the change in wording is in line with previous advice from the ESCs and MSAC. **REDACTED**

The ESCs considered that the department's proposed amendment of the item descriptor for the test as one to be requested 'by or on behalf of a specialist or consultant physician' was an acceptable means of ensuring adequate access to this item by general practitioners. The ESCs considered that the proposed item descriptor should take into consideration the uncertain turnaround time of NGS which could range from 6 to 8 weeks or beyond. The ESCs noted the proposed restriction of testing to once per primary tumour would mean that in the event of a test failure requiring re-testing, patients would incur out of pocket costs. The ESCs queried how this could be addressed. The ESCs noted that the submission did not provide justification for the proposed MBS fee of $2,200.

The ESCs noted that the test comparator was no testing, and that the treatment comparator was FULV monotherapy. However, the ESCs also noted that there was no standard of care (SOC) for this population and that a range of different treatment options was available. Therefore, the ESCs

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[12] P. 25 of 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 Confirmation,
http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C21E97CBD090988BCA258A6F00832B3E/$File/1766%20R atified%20PICO%20redacted.pdf

considered that FULV monotherapy alone might not be the most appropriate treatment comparator.

The ESCs considered that there was uncertainty in the diagnostic accuracy of testing, because there was no reference standard and the clinical utility standard used in the pivotal trial, FoundationOneCDx, was not available in Australia. The ESCs noted that concordance data comparing the clinical utility standard to the Roche Avenio CGP (an in-house NGS) and to non-specified 'externally validated NGS' tests (FDA 2019[13] and FDA 2023[14]) were provided. The studies showed good concordance; however, the ESCs considered that there was uncertainty in the concordance data. The comparison to the Roche assay was within only a small sample (21 patients, with 5 test failures and no patients who were negative for AKT pathway alterations). Regarding the FDA 2019 and FDA 2023 studies, the 'externally validated NGS test' used for comparison to FoundationOneCDx was not specified and the dataset for FDA 2019 tested patients for *PIK3CA* alterations only (i.e., did not test for *PTEN* or *AKT1* alterations); while the population for FDA 2023 included women with TNBC. The ESCs also considered that because the test likely to be used in practice in Australia was uncertain, it was not clear that the concordance data was representative of the expected test results in Australia. The ESCs noted that the pre-sub-committee response argued that because of National Association of Testing Authorities (NATA) accreditation, there would be no risk that a future NGS test used in Australia would give different results to the Roche AVENIO test proposed.

The ESCs noted that the submission did not address the concern raised by PASC: that the concordance data supplied by the applicant found that neither FoundationOneCDx nor AVENIO identified *PTEN* deletions. Therefore, the ESCs requested that the applicant provides primary data on *PTEN* deletion detection from available studies of NGS testing for MSAC consideration.

The ESCs noted that data supporting the prognostic ability of testing were provided from the SOC arms of 4 trials, and the most relevant studies were those that also used NGS (the CAPItello-291 and FAKTION trials). The ESCs noted that there appeared to be evidence that PFS and OS were shorter in patients with AKT pathway alterations, compared to patients with non AKT altered pathways. However, the ESCs noted that the differences in PFS and OS between patients with AKT altered and non AKT altered pathway were small, the 95% confidence intervals for PFS and OS were wide and overlapping, and considered that the OS data were immature. The ESCs also noted that the SOC in the trials was FULV+placebo, which might not be appropriate due to a number of alternative treatment options being available, as noted in the proposed clinical algorithm in the ADAR. These alternative options might have greater clinical benefit for patients than FULV monotherapy, and might be more commonly used in standard practice. Therefore, the ESCs considered that the estimated benefit of testing when compared only to FULV monotherapy might have been overestimated. As a result, the ESCs considered that the prognostic ability of testing was uncertain, and that a mixed SOC comparator would have been more informative.

In terms of predictive ability of testing, the ESCs noted that FAKTION included only a small number of patients tested using NGS, and that while CAPItello-291 was powered to examine differences in outcomes between treatment arms for the overall population as well as AKT pathway altered patients specifically, the treatment arms were not stratified by AKT status. The ESCs noted that in CAPItello-291, there was an overall benefit in PFS to CAPI+FULV treatment in all patient groups, with a stronger effect in those with AKT pathway alterations, but that there was also clinical benefit in the patient group without AKT pathway alteration. However, the ESCs noted that this patient group contained a relatively large number of patients with unknown AKT pathway status, and that *post hoc* analysis suggested that the benefit was not as pronounced in patients with known non AKT pathway alteration, although there was still a 21% reduction in hazard of progression for this patient group. The ESCs queried whether treatment might still be relevant to patients without AKT

[13] PMA P170019/S006: FDA Summary of Safety and Effectiveness Data
[14] PMA P170019/S048: FDA Summary of Safety and Effectiveness Data

pathway alterations, i.e., whether treatment would provide some clinical benefit for all patients regardless of AKT status, and therefore whether AKT testing should be required to access capivasertib. However, the ESCs also considered that, because AKT pathway alterations (particularly *PIK3CA* alterations) might be acquired over time, these results might have been reflective of the limitations of testing using archival tissue, and therefore a proportion of these patients might have harboured an acquired alteration (i.e. were false negatives). The ESCs therefore considered the predictive ability of testing, and whether or not it should be a requirement to access capivasertib, to be uncertain.

The ESCs noted that the OS data from CAPItello-291 was immature and did not show evidence of an OS benefit in any of the patient groups.

The ESCs noted that testing was performed on tissue, which could be undertaken using either archival tissue or fresh tissue. The ESCs noted that there was a risk of potential false negatives if testing was undertaken using the former whereas there were potential additional risks associated with a new biopsy if testing was undertaken with the latter, although the ESCs considered that these would be appropriately managed through standard processes in clinical settings. The ESCs noted that the main risk associated with false negative results was incurred through lack of treatment, but that the percentage of this was unknown, while the main risk of false positives was incurred through treatment followed by adverse events without benefit. The ESCs concluded that the ADAR's claim of inferior but manageable safety was reasonable.

The ESCs noted that the submission's overall clinical claim was that 'in patients with AI-resistant HR+/HER2- locally advanced or metastatic breast patients with confirmed AKT pathway altered (*PIK3CA*, *AKT1*, or *PTEN*) tumours, the addition of CAPI+FULV vs. FULV monotherapy led to statistically significant superior PFS outcome and inferior but manageable safety outcome'. The ESCs considered there to be uncertainty around the clinical effectiveness claim and clinical benefits of testing and treatment as well as further uncertainty around the predictive and prognostic benefits of testing for the reasons discussed above. Thus, the ESCs agreed with the commentary that there remained some uncertainty regarding the rationale for exclusion of patients who did not test positive to AKT pathway alteration from PBS funded treatment with CAPI+FULV. However, the ESCs advised that consideration should also be given to the fact that CAPI+FULV was inferior in safety compared with FULV monotherapy. Given potential safety concerns, treating patients without AKT pathway alterations, who are less likely to benefit from CAPI+FULV, may not be clinically appropriate.

The ESCs noted that the economic model compared the proposed test scenario followed by treatment with CAPI+FULV for AKT pathway altered patients and treatment with FULV+placebo, to no testing and all patients treated with FULV+placebo. The ESCs noted that the modelled time horizon was 15 years, but that the median follow-up in CAPItello-291 was 14-15 months. The ESCs acknowledged that 15 years might be clinically plausible for some patients, but considered that a shorter time horizon (5-10 years) might be more appropriate, given the short duration of follow-up in CAPItello-291 and the high level of uncertainty regarding longer term outcomes, particular OS. The ESCs noted that no convergence was included within the modelled Kaplan-Meier data, particularly in the OS model, so survival benefit increased over time. The ESCs considered that, in the case of OS, the model was highly optimistic, where the most optimistic function was chosen for the intervention arm and the least optimistic was chosen for the comparator, thereby overestimating the incremental survival benefit, with a hazard ratio more optimistic than the direct trial results.

The ESCs noted that the model assumed a test failure rate of 5% despite a failure rate of 15% in CAPItello-291, and that evidence was not provided to justify this assumption. The ESCs noted that the pre-sub-committee response stated that this was considered appropriate by a local clinical expert; however, as the test to be used in Australia is uncertain, the ESCs considered that there was not sufficient evidence to justify the lower test failure rate. The ESCs noted that increasing the failure rate had only a small effect on the incremental cost-effectiveness ratio (ICER), but that if the failure rate is higher in reality, health outcomes may have been overestimated in the model

(i.e. where patients of unknown status would not be eligible for treatment, and may have different prognosis to that assumed in the model).

The ESCs noted that the base case ICER from the stepped economic evaluation was $75,000 to <$95,000 per QALY gained, over the 15 year time horizon. The ESCs noted that sensitivity analyses demonstrated that test accuracy and test failure rate had only a small impact on the ICER. The ESCs noted the univariate sensitivity analyses conducted during the evaluation demonstrated that reducing the time horizon to 7 years increased the ICER by almost **redacted**%, and that changing the function used to model OS in both the treatment and comparator arm also significantly increased the ICER (by **redacted**%). The ESCs also noted that if no testing was performed, and patients were treated regardless of AKT pathway status, the ICER increased by **redacted**%. The ESCs considered that the chosen OS functions and time horizon were the key drivers of the model, and that a multivariate sensitivity analysis incorporating a shorter time horizon (of 7 to 10 years), increased failure rate (to 15%) and OS convergence would be beneficial.

The ESCs noted that the net cost to the MBS was estimated assuming an initial **redacted** in Year 6, resulting in a net cost of $0 to <$10 million in Year 1 and ~$0 to <$10 million in Year 6. However, the ESCs considered that the initial uptake rate was likely to be higher than 50%, noting that testing frequency and acceptance in this population is relatively high. This is because genetic testing is commonplace in breast cancer, and patients in the third line and beyond setting were excluded from the financial estimates despite being eligible for testing under the MBS item descriptor. The ESCs also noted that retesting scenarios were not considered in these financial estimates. These factors potentially resulted in underestimation of the impact on the MBS.

16. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website