Australian Government

Department of Health

RATIFIED PICO

Application 1604:

PIK3CA mutation testing for postmenopausal women or men with advanced breast cancer who have progressed during or following treatment with an aromatase inhibitor

Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	**Test population** Men and postmenopausal women with hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer, who have progressed on or after treatment with an aromatase inhibitor or a cyclin-dependent kinase inhibitor (CDKI) **Treatment population** Those patients above who test positive for a PIK3CA activating mutation
Prior tests	Tests required to confirm diagnosis of breast cancer (i.e. biopsy) Tests required to confirm stage of cancer (i.e. mammogram or ultrasound, lymph node assessment, computed tomography, magnetic resonance imaging) Tests required to confirm biomarker status: oestrogen receptor (ER) and progesterone receptor status (PR) to define HR status, and HER2 status
Intervention	**Test:** PIK3CA activating mutation testing **Treatment:** alpelisib combined with fulvestrant for patients found to have a PIK3CA mutation
Comparator	**Test comparator:** No testing for PIK3CA activating mutations **Treatment comparator:** Usual care: • First-line treatment if endocrine resistant (following adjuvant aromatase inhibitor treatment): CDKI + non-steroidal aromatase inhibitor (NSAI) or ribociclib + fulvestrant (optional) • Second-line treatment if CDKI + NSAI or aromatase inhibitor monotherapy failed: everolimus + exemestane or ribociclib + fulvestrant
Outcomes	***Test outcomes*** *Efficacy/effectiveness* Trial-based analytical performance of PIK3CA mutation testing • Diagnostic accuracy (Sensitivity, Specificity, PPV, NPV, etc) Comparative performance of PIK3CA mutation testing methods • Concordance between PIK3CA mutation testing assays • Re-testing rate *Safety outcomes* • Rate of re-biopsy • Adverse events related to testing

Component	Description

	Treatment outcomes
	Efficacy/effectiveness
	• Progression-free survival
	• Overall survival
	• Response rate
	• Quality of life
	
	Safety Outcomes:
	• Adverse events associated with subsequent treatment
	• Deaths
	
	Subgroup Analysis
	• Stratification by ER status and PR status
	
	Healthcare resources
	• Cost to deliver intervention
	  ○ Testing for PIK3CA activating mutations
	  ○ Re-biopsy
	
	Total Australian Government Healthcare costs
	• Total cost to the Medicare Benefits Schedule (MBS)
	• Total cost to the Pharmaceutical Benefits Scheme (PBS)
	• Total cost to other healthcare services

PICO or PPICO rationale for therapeutic and investigative medical services only

POPULATION

The proposed population for testing for a PIK3CA mutation comprises postmenopausal women and men with HR+/HER2– advanced breast cancer who have progressed on or after treatment with an aromatase inhibitor.

PASC noted the applicant is seeking an amendment to the PICO. The applicant is considering submitting to the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2020, for ribociclib plus fulvestrant for postmenopausal women or men with hormone receptor positive (HR+ve), human epidermal growth factor receptor 2 negative (HER2–ve) advanced breast cancer:

a. First-line – including patients with:
(i) assumed or known endocrine-sensitive disease (i.e. patients diagnosed de novo with advanced disease or patients treated with [neo-] adjuvant endocrine therapy who relapsed >12 months after treatment);
(ii) known endocrine-resistant disease (i.e. patients treated with [neo-] adjuvant endocrine therapy who relapsed on or within 12 months of treatment).

b. Second-line – including patients who failed treatment with an aromatase inhibitor in the first-line setting for advanced breast cancer.

PASC noted the applicant's amendment to the proposed test population (to include an alternative population): Men and postmenopausal women with HR+ve, HER2-ve advanced breast cancer, who have progressed on or after treatment with a cyclin-dependent kinase inhibitor (CDKI). The treatment population would remain unchanged. PASC noted that prior tests would also be unchanged.

PASC noted that a number of trials are underway in different settings and with different patient groups, with different drugs and different tests. Additional data and analyses will become available in 2020, to help determine the most appropriate place of alpelisib therapy (and hence the most appropriate timing of testing).

PASC advised that, if the place of alpelisib in the treatment pathway changes as a result of ribociclib PBS listing, this would affect population estimates, the clinical management algorithm and modelling. However, at this stage, it is unclear whether that would necessitate a major update or a change to information currently available.

PASC noted the final population will depend on whether PIK3CA testing is for first- or second-line treatment, and the assessment report/submission will cover both options.

PASC confirmed that 100% of women who present with HR+ve, HER2-ve advanced breast cancer would be considered post-menopausal, having received endocrine therapy, even if they were pre-menopausal at the time of diagnosis.

PASC noted the number for whom testing will be sought depends on assumptions about what proportion of patients would want to have the drug treatment. PASC also noted the test population would be reduced by the proportion of patients who have fulminant disease and go onto cytotoxic chemotherapy. PASC advised it would be useful to know the proportion of cases in each of these groups.

PASC noted the SOLAR 1 trial exclusion criteria (e.g. Eastern Cooperative Oncology Group performance-status score >1), which could apply to eligibility of the drug for PBS listing in the PBAC co-dependent submission.

PASC noted fulvestrant is not PBS-subsidised: funding for use of fulvestrant (in combination with alpelisib) will presumably be considered in the PBAC submission.

Background

Worldwide, breast cancer is the most common cancer diagnosed and the leading cause of cancer-related death in women (1). In Australia in 2018, it was estimated that 18,235 patients would be diagnosed with breast cancer (99.2% women), and 3,157 patients would die of their disease (99.1% women) (2). While breast cancer in men is rare, with less than one percent of breast cancer diagnoses in male subjects, treatment recommendations are the same for both the genders.

Based on expression of hormone receptors and HER2, breast cancer can be categorised into different histopathologic subtypes. Approximately 60-70% of breast tumours are HR+/HER2– (3).

Endocrine therapy is the treatment of choice for subjects with HR+ advanced breast cancer. Endocrine therapies include selective oestrogen receptor (ER) modulators (SERMs; e.g. tamoxifen),

selective non-steroidal aromatase inhibitors (NSAI; e.g. letrozole and anastrozole), steroidal aromatase inhibitors (e.g. exemestane), and ER antagonists (e.g. fulvestrant) (4).

Endocrine therapy may be given in first, second, or later lines of therapy for advanced breast cancer. Progressive disease ultimately develops in all subjects, either due to primary resistance (de novo resistance) or relapse/progression following an initial response (acquired resistance). Despite significant advances in treating subjects with HR+ breast cancer, the development of endocrine resistance (and hence disease progression) remains a critical problem (5). New therapies with improved efficacy, ideally paired with predictive biomarkers to allow selection of subjects who would benefit the most, are therefore required.

Two new classes of targeted compounds have demonstrated clinical efficacy when combined with endocrine therapy and obtained regulatory approvals in HR+/HER2– advanced breast cancer: (i) mammalian target of rapamycin (mTOR) inhibitors, e.g. everolimus, and (ii) cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, e.g. palbociclib, ribociclib, and abemaciclib) (6). No predictive biomarkers have been identified to select patients that would benefit the most from these therapies to date (7).

PIK3CA activating mutations in breast cancer

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mTOR pathway is postulated to be a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival, and apoptosis. The PI3K pathway may be activated by gain of function mutations and/or amplification of the PIK3CA gene (8). PI3K signalling is known to be a critical step in mediating the transforming potential of oncogenes and tumour suppressors in many tumour types (9), and changes in PI3K activity are associated with resistance to endocrine, chemo-, radio-, and anti-HER2 therapies (10). Targeted therapy with a PIK3CA inhibitor could therefore be considered a potentially valuable treatment option for subjects with HR+ advanced breast cancer with a PIK3CA mutation that has developed resistance to prior endocrine treatment.

PIK3CA activating mutations are reported in approximately 45% of HR+/HER2– breast cancers (11). Multiple PIK3CA hotspot mutations can be found on exons 7, 9 and 20. The SOLAR 1 trial used the Qiagen *therascreen*® RGQ PCR tissue test (CDx) as the main test for PIK3CA mutations, although a proportion of patients were also tested with the Roche cobas® PCR test (CTA).

In addition, a plasma test was also conducted on all patients using the Qiagen *therascreen*® RGQ PCR plasma test. The three tests targeted different PIK3CA mutations, and the prevalence of the mutations found also differed between the tests. The most commonly found individual PIK3CA mutations were E542K, E545K and H1047R. It should be noted that the rate of PIK3CA mutations in the SOLAR 1 trial was substantially higher than that reported by the Cancer Genome Atlas Network (60% versus 45%). This may be due to the narrower population included in the SOLAR 1 trial, who in addition to being HR+/HER2– also had to have experienced recurrence or progression of their breast cancer during or after treatment with an aromatase inhibitor.

Estimates for size of the testing population

As shown in Table 1, it is estimated that approximately 2,500 patients would be eligible for PIK3CA testing in 2019, representing about 5% of the total prevalent breast cancer population. However, it is important to note the following about the assumptions used in these calculations:

- The proportion of patients who are postmenopausal is likely to be higher than literature estimates of 87% (12). Australian clinicians have advised that most pre-menopausal patients in the advanced breast cancer setting will have either oophorectomy or reversible treatment options such as ovarian radiation or treatment with luteinizing hormone-releasing hormone agonist (LHRHa) (goserelin acetate or leuprolide acetate) for the induction of ovarian suppression to ensure access to the most effective treatment options. The PBS criteria for ribociclib does not specify method for induction of menopause.
- It assumes almost all patients will receive aromatase inhibitors and will eventually develop resistance (either in the adjuvant or advanced breast cancer setting).
- It assumes 100% of patients who develop resistance would be considered for treatment with alpelisib, and does not take into account patients who do not meet the additional clinical criteria for alpelisib treatment defined in the SOLAR 1 trial, including adequate bone marrow and organ function, and no diagnosis of Type I diabetes or uncontrolled Type II diabetes.

Table 1. **REDACTED**

Prior tests

Patients with HR+/HER2- advanced breast cancer would require prior testing before they can become eligible for PIK3CA mutation testing. These prior tests include:

- biopsy and imaging (mammogram, ultrasound or magnetic resonance imaging (MRI)) to confirm diagnosis of breast cancer
- staging workup, which is guided by symptoms and may include clinical and ultrasound assessment of lymph nodes, computed tomography, bone scan, x-rays, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography–computed tomography
- molecular diagnostic studies including:
    - immunohistochemical evaluation of hormone receptor (HR) status
    - immunohistochemical evaluation to determine HER2 status

INTERVENTION

PASC noted the intervention, which does not specify a particular testing methodology, will be unchanged if the applicant proceeds with a PBAC submission for ribociclib.

PASC noted the two commercial tests (Qiagen therascreen®-CDx [tissue or plasma]; and Roche Cobas-CTA [tissue]), used in the SOLAR 1 clinical trial, identified different PIK3CA gene mutations, with only some identified by both tests (Table 1 in the Application Form).

The applicant has advised that the above statement is incorrect. The applicant has stated that the only difference in mutations tested is Q546K (which is included in the Roche test, but not the Qiagen test). The lack of 'ticks' in the Roche Cobas column of the table is because the Roche cobas test groups some mutations together and reports them under a single identifier, as described in the table footnotes; i.e. E545X includes E542A, D, G, and K; Q546X includes Q546E, K and R and H1047X includes H1047L, R and Y.

PASC noted neither of the tests used in the trial are currently registered with the TGA, and Australian laboratories use locally-developed methods for PIK3CA testing. PASC noted the applicant's statement that details of exact methodologies likely to be used in Australia will be gathered from laboratories and presented in the co-dependent assessment report/submission.

PASC noted the applicant's statement that current tests detect hotspot mutations, which account for about 82% of mutations, and there is no viable immunohistochemistry triage method available.

PASC noted the rate of PIK3CA mutations in the SOLAR 1 trial was substantially higher than the rate reported by the Cancer Genome Atlas Network (60% vs 45%), which may be due to patient selection in the trial being based on failed prior treatment.

PASC noted the choice of tumour or plasma as the test sample (and when and how often testing is done), will affect the PICO, modelling and MBS item descriptor. PASC noted the applicant is planning to investigate different testing scenarios (i.e. before second-line treatment for advanced breast cancer; before first- and second-line treatment; and with or without the option of plasma testing), in terms of the best option for patients and cost-effectiveness.

PASC favoured testing of tumour tissue, because that is the evidentiary standard (used in the SOLAR 1 trial), but noted that plasma testing may be required in some situations (if fresh or archived tissue is not available).

PASC noted the applicant's statement that, because of the frequency of PIK3CA mutations, a plasma test does not need to be highly sensitive, and the PPV and NPV would be expected to be higher than for other mutations. PASC advised that plasma testing should be evaluated separately, including the false negative rate.

PASC considered that including plasma testing opens up many other issues (e.g. multiplicity issues), and has implications for service provision, access, staff and costs.

PASC queried whether a biopsy would be required at the time of recurrence, in order to obtain a fresh tissue sample (due to biomarker instability). PASC noted the applicant's statement that, because PIK3CA is a driver mutation, it will be carried forward with cancer progression, and endocrine treatment can drive PIK3CA mutations to increase. However, it is not uncommon for mutations to arise in the metastatic site, especially in the context of endocrine resistance. Re-biopsy may therefore be required. PASC advised that the assessment report/submission should address the downline consequences if re-biopsy is needed.

The application is co-dependent, for MBS listing of PIK3CA activating mutation testing, to determine which patients with HR+/HER2- advanced breast cancer (who have progressed on or after treatment with an aromatase inhibitor) have a PIK3CA mutation, and may therefore be eligible for treatment with alpelisib (combined with fulvestrant).

PIK3CA mutation testing

Testing for PIK3CA mutations can be performed on either tissue or plasma samples. Testing for PIK3CA mutation would be preferentially performed using fresh tissue, biopsied at the site of local recurrence or metastasis, but archival tissue could be used instead. The biopsy would typically be performed, and testing requested, by a surgeon or oncologist.

Testing would be performed in a National Association of Testing Authorities, Australia (NATA)-accredited laboratory on sections obtained from Formalin Fixed Paraffin Embedded (FFPE) blocks. Laboratory staff involved in the testing process would include anatomical pathologists, scientists and technicians.

Where a tissue sample is readily available:

- Identification of a PIK3CA mutation would result in a patient being eligible for treatment with alpelisib (in combination with fulvestrant)
- No identification of a PIK3CA mutation would result in patients being eligible to receive usual care.

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

Following testing of a plasma sample:

- Identification of a PIK3CA mutation would result in a patient being eligible for treatment with alpelisib (in combination with fulvestrant)
- No identification of a PIK3CA mutation would result in patients needing a tissue biopsy for further consideration for treatment with alpelisib (in combination with fulvestrant), due to the rate of false negatives using the plasma compared with the tissue test.

Delivery

Two commercial tests using multiplexed qualitative real time PCR assays were used in the SOLAR 1 clinical trial to identify patients with a PIK3CA mutation:

- CTA – Clinical Trial Assay - performed using the *Novartis CTA PCR Kit* on the cobas® z480 analyzer with the cobas® 4800 SR2 System Control Unit and System Software.
- CDx – Companion Diagnostic - performed using the *QIAGEN therascreen® PIK3CA RGQ PCR Kit* and Rotor-Gene® Q (RGQ) MDx instrument with 72-well rotor with the RGQ Open Mode Software.

Neither PIK3CA assay kit is currently registered with the TGA, although other cobas-related tests are.

Setting

Australian laboratories currently performing PIK3CA testing use locally-developed methods. Details of exact methodologies likely to be used in Australia, as well as single and multi-use consumables, will be gathered from laboratories and presented in the co-dependent assessment report/submission.

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

COMPARATOR

PASC confirmed "no testing for PIK3CA activating mutations" as the test comparator. PASC confirmed "usual care" as the treatment comparator, but noted usual care is complex, given the clinical place of therapies is uncertain with emerging new drugs.

PASC noted the applicant's proposed amendments to the comparator, as a result of their potential PBAC submission for ribociclib:

> *– First-line treatment, if endocrine-resistant following (neo-) adjuvant aromatase inhibitor treatment: CDKI + NSAI or ribociclib + fulvestrant (optional)*
>
> *– Second-line treatment, if CDKI + NSAI or aromatase inhibitor monotherapy failed: everolimus + exemestane or ribociclib + fulvestrant*

PASC noted the applicant is still investigating whether to proceed with including a first-line indication, or limit to a second-line treatment indication.

Comparator for PIK3CA activating mutations testing

The nominated comparator is **no testing** for PIK3CA activating mutations**.**

Comparator for treatment

The comparator for alpelisib combined with fulvestrant is treatment with **usual care**. Usual care is complex, made up of a 'basket' of different treatment options as outlined below. The relative proportions of patients currently receiving each treatment option will be examined during preparation of the co-dependent assessment report/submission.

- For first-line treatment of advanced breast cancer where patients are considered endocrine resistant following adjuvant aromatase inhibitor therapy (i.e. relapse occurred while on aromatase inhibitor treatment) the following treatments are currently used in Australia:
    - CDKI (ribociclib or palbociclib) + NSAI (anastrozole or letrozole) or ribociclib + fulvestrant (optional).
- For second-line treatment of advanced breast cancer (i.e. where patients have failed first-line treatment with either CDKI + NSAI or aromatase inhibitor monotherapy) the following treatments are used:
    - Everolimus plus exemestane
    - Ribociclib + fulvestrant.

The lines of therapy and associated treatment options are presented in the Current Clinical Pathway algorithm (Figure 1). It should be noted that while chemotherapy and best supportive care are also treatment options, they are generally reserved for patients with visceral crisis or those not considered suitable for the treatments outlined above, and so are used in a separate patient subgroup.

OUTCOMES

PASC advised that the applicant's submission/assessment report will need to prove that, regardless of how the mutation is detected, the clinical outcome for the patient is the same.

The applicant has advised that it will be possible to show clinical outcome based on test methodologies used within the SOLAR-1 trial (Roche cobas, Qiagen tissue test and Qiagen plasma test), but not against other testing methodologies. The applicant confirms that concordance between other testing methodologies and those shown above will be examined, which is consistent with MSAC assessments on other test/treatment pairings.

PASC noted the PIK3CA test is considered to be robust, so concordance should not be a problem. PASC noted that indirect evidence for concordance between different types of tests and samples will be provided in the assessment report/submission.

PASC advised that the assessment report/submission should address the consequences of discordance (e.g. the biological plausibility that any discordant cell should not be treated).

Where available, direct evidence of the effectiveness of the test-treatment combination should be used. This direct evidence can be obtained in test-treatment trials where patients are:

- randomly allocated to PIK3CA testing or comparator (no PIK3CA testing); then randomised to use of alpelisib plus fulvestrant or usual care; and the outcome measured at follow-up
- randomly allocated to PIK3CA testing or comparator (no PIK3CA testing), treated according to test result and following pre-specified treatment plans, and the outcome measured at follow-up
- prospectively tested for PIK3CA mutation; then those testing positive randomised to use of alpelisib plus fulvestrant or usual care; and the outcome measured at follow-up
- randomly allocated to the use of alpelisib plus fulvestrant or usual care; the outcome measured at follow-up; then the results analysed across subgroups of patients defined by whether a PIK3CA mutation was present or not.

However, direct evidence is not always available, and a linked evidence approach or elements of a linked evidence approach may be needed (see page 194 of MSAC guidelines). The linked evidence approach includes assessing the analytical test performance (diagnostic accuracy) and change in clinical management because of knowledge of test result.

It should be noted that a linked evidence approach for PIK3CA mutation testing is complicated by the fact that generally no reference standard exists for genetic tests. In this situation, the diagnostic accuracy of a test (i.e. test sensitivity and specificity) cannot be calculated. Measures of concordance or agreement between different PIK3CA mutation tests can provide an estimate of test performance, however these comparisons of non-reference tests are less informative.

The applicant nominated the following outcomes:

Test outcomes

Efficacy/effectiveness

- Trial-based analytical performance of PIK3CA mutation testing
- Diagnostic accuracy (Sensitivity, Specificity, PPV, NPV, etc)

Comparative performance of PIK3CA mutation testing methods

- Concordance between PIK3CA mutation testing assays
- Re-testing rates

Safety outcomes

- Rate of re-biopsy
- Adverse events related to testing

Treatment outcomes

The assessment of outcomes regarding treatment with alpelisib (combined with fulvestrant) is the remit of PBAC. However, for the purpose of this co-dependent MSAC/PBAC application, the following treatment outcomes apply:

Efficacy/effectiveness

- Progression-free survival
- Overall survival
- Response rate
- Quality of life

Safety Outcomes:

- Adverse events associated with subsequent treatment
- Deaths

Healthcare resources

- Cost to deliver intervention
    - Testing for PIK3CA activating mutations
    - Re-biopsy

Total Australian Government Healthcare costs

- Total cost to the Medicare Benefits Schedule (MBS)
- Total cost to the Pharmaceutical Benefits Scheme (PBS)
- Total cost to other healthcare services

CLINICAL MANAGEMENT ALGORITHMS

PASC noted the applicant's PBAC submission for ribociclib may change the placement of alpelisib therapy, and therefore placement of the test to access therapy, which will require revised algorithms.

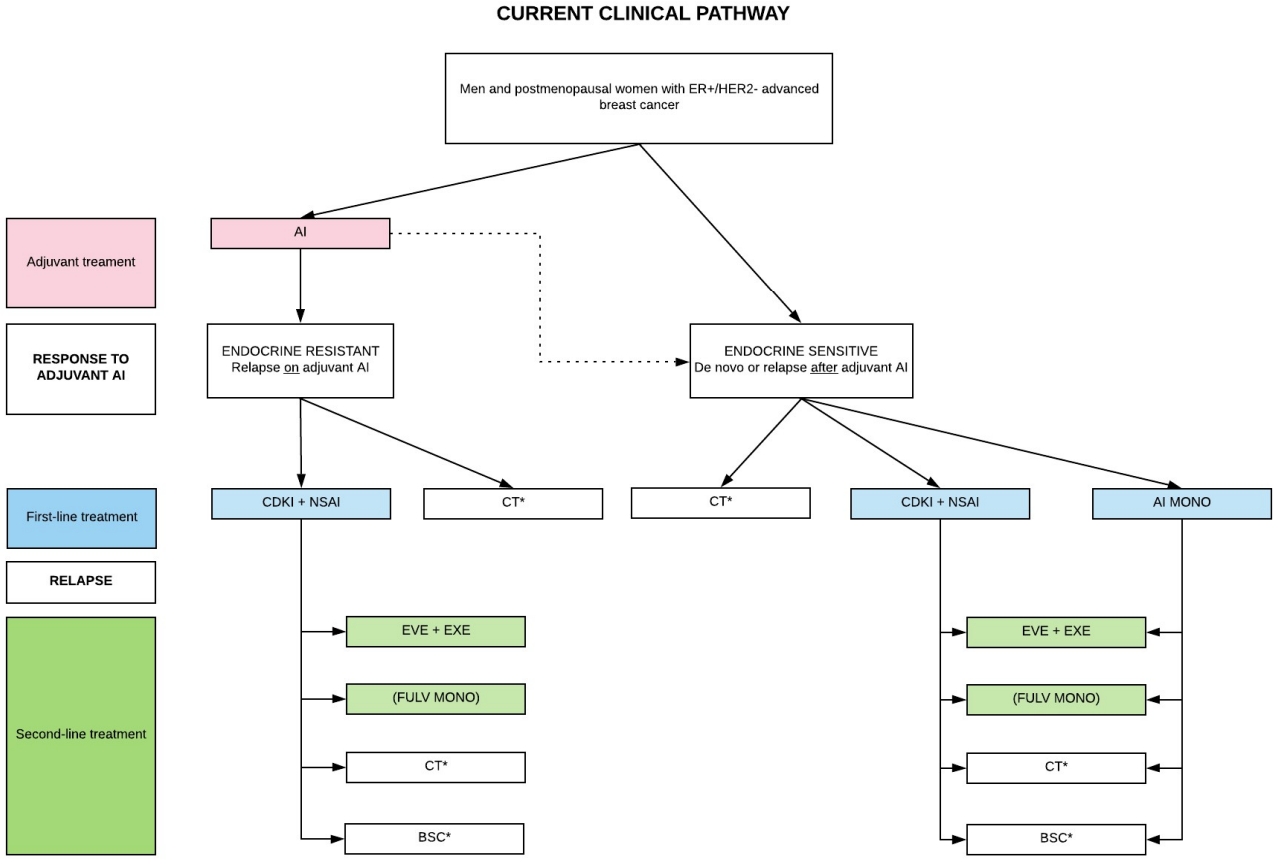
PASC also noted the population size will be different in each algorithm, depending on whether testing is for first- or second-line treatment. PASC advised that the evaluation should evaluate both options.

The applicant has advised that they may decide against the first-line option before or during the preparation of the ADAR. In that case, the first-line treatment option will not be evaluated and an explanation of why this is the case will be included.

Current clinical management algorithm for identified population

As shown in Figure 1, there are a number of treatment options available in the second-line setting. Patients may subsequently move between these treatment options for later lines of therapy, including moving to best supportive care.

Figure 1. Current clinical management algorithm



Abbreviations: AI, aromatase inhibitor; BSC, best supportive care; CDKI, cyclin-dependent kinase inhibitor; CT, chemotherapy; ER+, oestrogen receptor-positive; EVE, everolimus; EXE, exemestane; FULV, fulvestrant, HER2-, human epidermal growth factor receptor 2-negative; MONO, monotherapy; NSAI, non-steroidal aromatase inhibitor.
* Generally reserved for patients with visceral crisis or who are not considered suitable candidates for the highlighted treatments.

Proposed clinical management algorithm for identified population

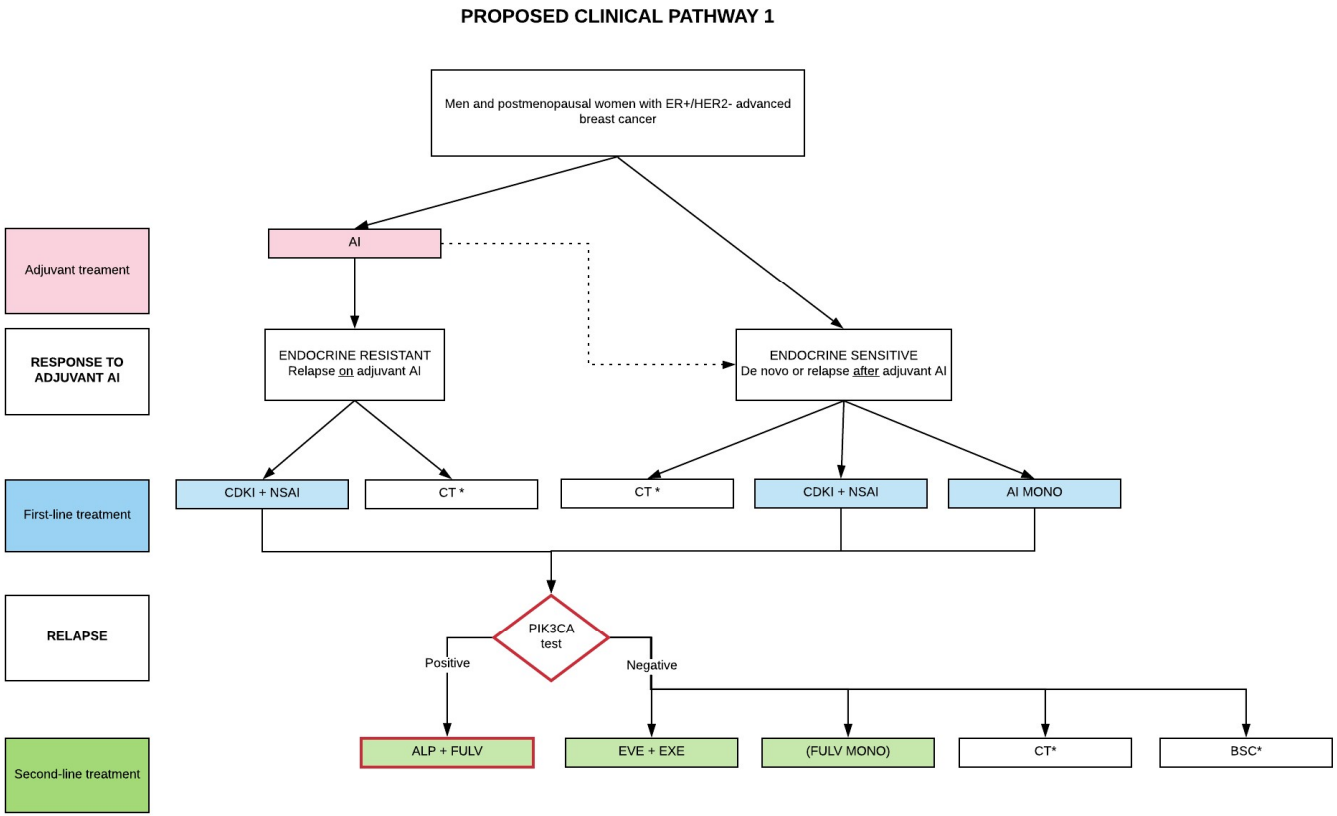
Two Proposed Clinical Pathways are presented: (i) including PIK3CA testing to inform second-line advanced breast cancer treatment with alpelisib (Figure 2) and (ii) including PIK3CA testing to inform first- and second-line advanced breast cancer treatment with alpelisib (Figure 3).

As noted previously, the Proposed Clinical Pathway includes two possible scenarios. The first scenario is the ability to test for PIK3CA mutations prior to initiation of second-line (or first- and second-line) therapy for advanced breast cancer, with patients with PIK3CA mutation positive advanced cancer receiving treatment with alpelisib (in combination with fulvestrant).

The second scenario is the ability to test patients with PIK3CA mutation negative advanced breast cancer receiving treatment with usual care (which includes a number of different treatment options).

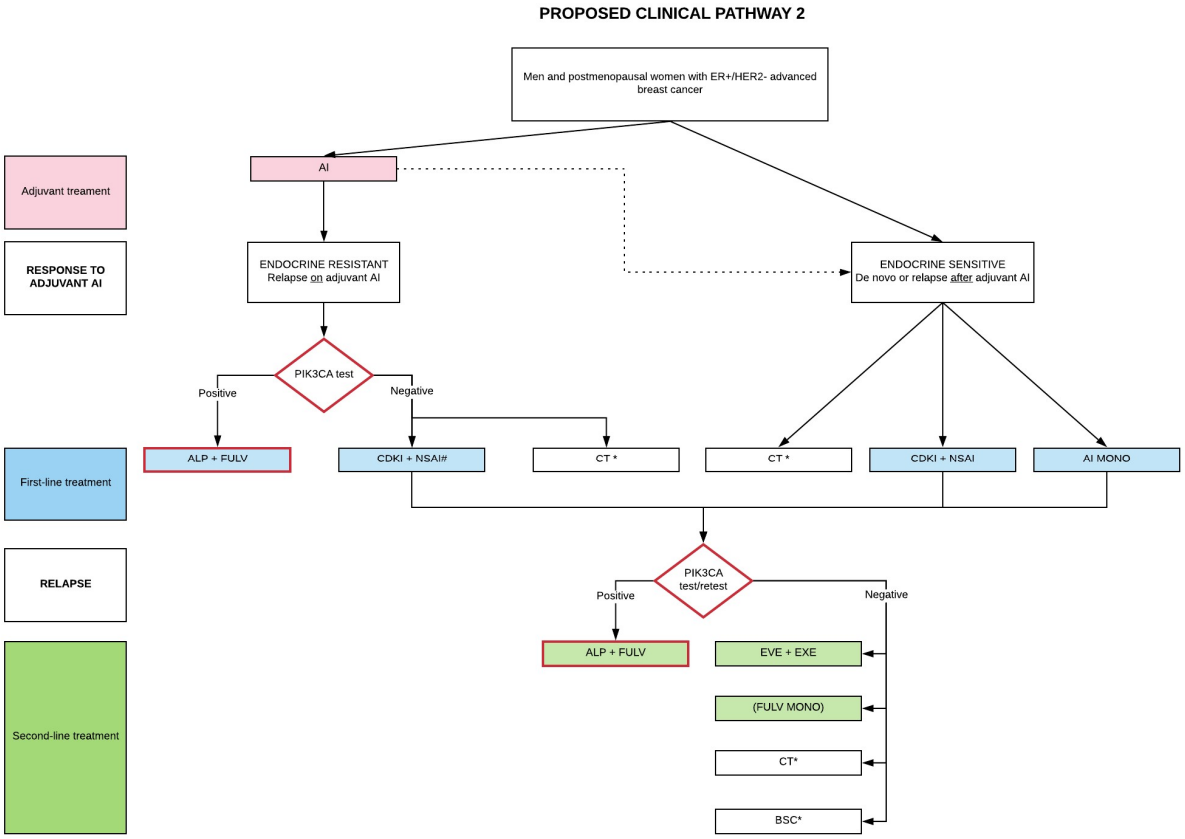
The inclusion of PIK3CA testing and treatment with alpelisib presented in the Proposed Clinical Pathways is consistent with recent changes to the NCCN Guidelines Version 2.2019 Invasive Breast Cancer (as shown in Attachment B). Within the NCNN Guidelines Version 2.2019, testing for PIK3CA mutation is included in the work-up for patients with recurrent or stage IV invasive HR+/HER2– breast cancer, and alpelisib plus fulvestrant is included in the list of preferred treatment options for PIK3CA-mutated tumours in postmenopausal patients with HR+/HER2– recurrent or stage IV invasive breast cancer.

Figure 2. Proposed clinical management pathway 1 – PIK3CA testing and treatment with alpelisib combined with fulvestrant (second-line only)



Abbreviations: AI, aromatase inhibitor; BSC, best supportive care; CDKI, cyclin-dependent kinase inhibitor; CT, chemotherapy; ER+, oestrogen receptor positive; EVE, everolimus; EXE, exemestane; FULV, fulvestrant, HER2-, human epidermal growth factor receptor 2 negative; MONO, monotherapy.; NSAI, non-steroidal aromatase inhibitor.
* Generally reserved for patients with visceral crisis or who are not considered suitable candidates for the highlighted treatments.

Figure 3. Proposed clinical management pathway 2 – PIK3CA testing and treatment with alpelisib combined with fulvestrant (first- and second-line)



Abbreviations: AI, aromatase inhibitor; BSC, best supportive care; CDKI, cyclin-dependent kinase inhibitor; CT, chemotherapy; ER+, oestrogen receptor positive; EVE, everolimus; EXE, exemestane; FULV, fulvestrant, HER2-, human epidermal growth factor receptor 2 negative; MONO, monotherapy; NSAI, non-steroidal aromatase inhibitor.
Some patients may develop PIK3CA mutations following treatment with a CDKI, so these patients may need to be retested.
* Generally reserved for patients with visceral crisis or who are not considered suitable candidates for the highlighted treatments.

PROPOSED ECONOMIC EVALUATION

PASC confirmed the economic evaluation should be a cost-effectiveness/cost-utility analysis.

PASC noted the applicant's statement that cost-effectiveness analysis will be finalised after the PICO is clarified.

The overall clinical claim is for superiority. The applicant has claimed that the proposed co-dependent technology (PIK3CA activating mutation testing and alpelisib/fulvestrant treatment) is superior in terms of comparative effectiveness versus the main comparator (no testing and usual care) in men and postmenopausal women with HR+/HER2- advanced breast cancer, who have progressed on or after treatment with an aromatase inhibitor. According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative* the required economic analysis is therefore a cost-utility or a cost-effectiveness analysis. However, if the evidence does not prove superiority or non-inferiority, then a cost-consequence model may be more appropriate.

PROPOSED MBS ITEM DESCRIPTOR/S AND MBS FEES

PASC noted that many drugs acting on PI3K/AKT/mTOR pathway are in the pipeline, and some of these may be relevant to PIK3CA testing in the future.

PASC favoured a generic MBS item descriptor, rather than limiting it to alpelisib (acknowledging that MSAC may prefer to specify the drug name). MSAC will decide on final descriptor wording.

The applicant has advised that their understanding is that, in cases where testing is linked to use of a particular drug, the MBS item descriptor will always specify the drug name.

PASC advised that a change to the item descriptor would be required if prior treatment is (or may be) CDKI (depending on the PBAC submission for ribociclib).

PASC advised that a revised item descriptor is required if testing is to be done for first-line treatment (depending on the PBAC submission for ribociclib).

PASC advised that, even if testing is to be done for first-line treatment, some evidence of resistance to endocrine therapy will probably be required.

The applicant has advised that evidence of resistance to (neo)adjuvant treatment with an aromatase inhibitor is currently required for eligibility for first-line testing for PIK3CA, as reflected in the treatment algorithm included in the PICO.

PASC advised that frequency of testing should be specified, and if it includes repeat testing, the assessment report/submission will need to justify the frequency.

PASC noted the item descriptor currently specifies "tumour tissue" as the sample. PASC advised this will need to be revised if plasma testing is to be included.

PASC advised that the item descriptor should use "activating variant", not "activating mutation".

Proposed item descriptor:

Category 6 – PATHOLOGY SERVICES
A test on tumour tissue from a postmenopausal woman or man with advanced breast cancer who has progressed on or following treatment with an aromatase inhibitor, requested by, or on behalf of, a specialist or consultant physician, to determine if requirements relating to PIK3CA activating variant status for access to alpelisib under the Pharmaceutical Benefits Scheme are fulfilled. MBS Fee: To be determined

CONSULTATION FEEDBACK

PASC noted the supportive consultation feedback from the Royal College of Pathologists of Australasia (RCPA) and Breast Cancer Network Australia (BCNA).

NEXT STEPS

Upon ratification of PICO 1604, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage.

The applicant has elected to prepare its own ADAR (applicant-developed assessment report).

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2018;4(11):1553-68.

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