Australian Government

Department of Health

Application Form

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

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Novartis Pharmaceuticals Australia Pty Ltd

Corporation name: **REDACTED**

ABN: R**EDACTED**

Business trading name: **REDACTED**

Primary contact name: REDACTED

Primary contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name REDACTED

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

Not applicable

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

PIK3CA testing for postmenopausal women and men with hormone receptor positive (HR+)/human epidermal growth factor negative (HER2–) advanced breast cancer that has progressed on or after treatment with an aromatase inhibitor

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Worldwide, breast cancer is the most common cancer diagnosed in women and the leading cause of cancer-related death in women (Global Burden of Disease Cancer Collaboration 2018).[1] In 2018 in Australia, an estimated 18,235 new cases of breast cancer were diagnosed, more than any other cancer type.[2] Approximately 60-70% of breast tumours are HR+/HER2–.[3] While endocrine therapy is the treatment of choice for subjects with HR+ advanced breast cancer, progressive disease ultimately develops in all subjects, either due to primary resistance or relapse/progression following an initial response. Two new classes of targeted compounds (mammalian target of rapamycin (mTOR) inhibitors, and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors) have demonstrated clinical efficacy when combined with endocrine therapy. However, to date no predictive biomarkers have been identified to select patients that would benefit the most from these therapies.[4]

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

The PI3K/AKT/mTOR pathway is postulated to be a central oncogenic pathway that regulates cell proliferation, cell metabolism, growth, survival, and apoptosis. Changes in PI3K activity are associated with resistance to endocrine, chemo-, radio-, and anti-HER2 therapies.[5] PIK3CA mutations are reported in up to 45% of HR+/HER2 breast cancers.[6] The results of the SOLAR 1 clinical trial demonstrate a substantial clinical benefit of alpelisib plus fulvestrant compared with fulvestrant alone in PIK3CA mutation-positive patients who have progressed on or after an endocrine-based regimen. Thus, the proposed medical service is testing for PIK3CA mutation in this population.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

Not applicable

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[1] Global Burden of Disease Cancer Collaboration (2018) 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 Oncology 4(11): 1553-1568.

[2] breast-cancer.canceraustralia.gov.au/statistics.

[3] O'Brien et al (2010) Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clin Cancer Research; 16(24): 6100-10.

[4] Pernas et al (2018) CDK4/6 inhibition in breast cancer: current practice and future directions. Ther Adv Med Oncol; 10:1-15; Shah and Dickler (2014) Endocrine therapy for advanced breast cancer. Clin Adv Hematol Oncol; 12(4): 214-2; Hortobagyi et al (2016) Ribociclib as first-line therapy for HR-positive, advanced Breast Cancer. N Engl J Med; 375(18):1738-48.

[5] Keegan et al (2018) PI3K inhibition to overcome endocrine resistance in breast cancer. Expert Opin Invest Drugs; 27(1):1-15.

[6] Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumors. Nature; 490(7418):61-70.

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

Not applicable

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

No other source of public funding for PIK3CA mutation testing, other than the MBS, will be sought. However, this application will be part of a codependent submission where public funding on the PBS for alpelisib (to be used in combination with fulvestrant) will be sought for eligible patients.

(g) If yes, please advise:

Not applicable

7. What is the type of service:

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☒ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

Not applicable

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☒ No

A codependent submission requesting reimbursement for the use of alpelisib (in combination with fulvestrant) in postmenopausal women and men with HR+/HER2– advanced breast cancer that has progressed on or after treatment with an aromatase inhibitor, supported by data from the SOLAR 1 trial, is planned for REDACTED, in accordance with the codependent submission timelines.

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: Piqray®
Generic name: alpelisib

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

Not applicable

(b) If yes, please provide the following information (where relevant):

Not applicable

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

Not applicable

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

Not applicable

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

Not applicable

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Australian laboratories currently performing PIK3CA testing use locally developed methods. Details of the exact methodologies likely to be used in Australia, as well as any single and multiuse consumables will be gathered from laboratories during the preparation, and presented in, the codependent submission.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

The proposed medical service, PIK3CA mutation testing, does not specify a particular methodology. As noted in Q12, Australian laboratories currently performing PIK3CA testing use locally developed methods. Details of the exact methodologies likely to be used in Australia will be gathered from laboratories during the preparation of the full co-dependent submission dossier.

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.

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☐ Yes (if yes, please provide details below)
☒ No

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☐ Yes (please provide details below)
☒ No

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

☒ Yes (please provide details below)
☐ No

Estimated date of submission to TGA: REDACTED
Proposed indication(s), if applicable: Not applicable
Proposed purpose(s), if applicable: REDACTED

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)**	**Website link to journal article or research (if available)**	**Date of publication**
Alpelisib clinical study					
1	Phase III randomised controlled trial	Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer SOLAR 1 trial/CBYL719C2301 NCT02437318	The combination of alpelisib and fulvestrant prolonged progression-free survival compared with placebo plus fulvestrant in men and postmenopausal women with HR+/HER2– advanced breast cancer which progressed on or after aromatase inhibitor treatment who had a PIK3CA mutation. A total of 572 patients were randomised. PIK3CA mutation status was measured using two different tissue real PCR tests (CDx and CTA) and one plasma real PCR test (CDx).	www.ncbi.nlm.nih.gov/pubmed/31091374	André 2019

	Type of study design	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)	Website link to journal article or research (if available)	Date of publication
PIK3CA testing studies					
Tests directly compared against the evidentiary standards - tissue CDx (Qiagen therascreen) and tissue CTA (Roche cobas)					
2	RCT	A Phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment: Summary of PIK3CA Mutation Testing CBYL719C2301	A companion summary report to the SOLAR 1 CSR outlining the findings of the PIK3CA testing in terms of diagnostic performance and clinical outcome. **Tissue real time PCR CDx (Qiagen therascreen) vs tissue real time PCR CTA (Roche cobas)** N=395 **Tissue real time PCR CDx (Qiagen therascreen) vs plasma real time PCR CDx (Qiagen therascreen)** N=549	Not available	Dec 2018
3	Observational/ diagnostic	PIK3CA mutations may be discordant between primary and corresponding metastatic disease in breast cancer	Assessed diagnostic performance only **Tissue real time PCR CDx (Qiagen therascreen) vs SNaPshot PCR** N=21	www.ncbi.nlm.nih.gov/pubmed/20940279	Jensen 2011

	Type of study design	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)	Website link to journal article or research (if available)	Date of publication
4	Observational/ diagnostic	Comparison of Three Real-Time PCR Assays for the Detection of PIK3CA Somatic Mutations in Formalin-Fixed Paraffin Embedded Tissues of Patients with Breast Carcinomas	Assessed diagnostic performance only **Tissue real time PCR CTA (Roche cobas) vs ARMS/Scorpion PCR** N=45 **Tissue real time PCR CTA (Roche cobas) vs HRM** N=45	www.ncbi.nlm.nih.gov/pubmed/30426328	Lambert 2018
5	RCT	Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): a randomised, double-blind, placebo-controlled, phase 3 trial BELLE-3	Clinical performance of buparlisib plus fulvestrant and diagnostic performance of PIK3CA testing **Tissue real time PCR CTA (Roche cobas) vs plasma BEAMing PCR** N=256	www.ncbi.nlm.nih.gov/pubmed/29223745	Di Leo 2018
Tests compared against other tests					

	Type of study design	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)	Website link to journal article or research (if available)	Date of publication
6	Observational/ diagnostic	PIK3CA mutation profiling in patients with breast cancer, using a highly sensitive detection system	Diagnostic performance of PIK3CA testing and prognostic impact **Tissue ddPCR vs tissue direct sequencing** N=30 **Tissue ddPCR vs tissue QP system** N=30	www.ncbi.nlm.nih.gov/pubmed/29906308	Shimoi 2018
7	RCT	Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial BELLE-2	Clinical performance of buparlisib plus fulvestrant and diagnostic performance of PIK3CA testing **Tissue sanger sequencing vs plasma BEAMing PCR** N=582	www.ncbi.nlm.nih.gov/pubmed/28576675[7]	Baselga 2017

[7] Concordance data is from the Supplementary Appendix.

	Type of study design	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)	Website link to journal article or research (if available)	Date of publication
8	Observational/ diagnostic	Phase I/II dose-escalation study of PI3K inhibitors pilaralisib or voxtalisib in combination with letrozole in patients with hormone-receptor-positive and HER2-negative metastatic breast cancer refractory to a non-steroidal aromatase inhibitor	Clinical performance of pilaralisib or voxtalisib in combination with letrozole and diagnostic performance of PIK3CA testing **Tissue NGS vs plasma BEAMing PCR** N=31	www.ncbi.nlm.nih.gov/pubmed/26497877	Blackwell 2015
9	Observational/ diagnostic	Concordance of Genomic Alterations by Next-Generation Sequencing in Tumor Tissue versus Circulating Tumor DNA in Breast Cancer	Assessed diagnostic performance only **Tissue NGS vs plasma NGS** N=45	www.ncbi.nlm.nih.gov/pubmed/28446639	Chae 2017
10	RCT	A randomized phase II trial of trastuzumab plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxanes: WJOG6110B/ELTOP	Clinical performance of trastuzumab plus capecitabine versus lapatinib plus capecitabine and diagnostic performance of PIK3CA testing **Tissue ddPCR vs plasma ddPCR** N=26	www.ncbi.nlm.nih.gov/pubmed/29698927	Takano 2018

	Type of study design	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)	Website link to journal article or research (if available)	Date of publication
11	Open-label Phase I-II /clinical	Phase I/II clinical trial of everolimus combined with gemcitabine/cisplatin for metastatic triple-negative breast cancer	Clinical performance of everolimus combined with gemcitabine/cisplatin and diagnostic performance of PIK3CA testing **Tissue ddPCR vs plasma ddPCR** N=23	www.ncbi.nlm.nih.gov/pubmed/29675095	Park 2018
12	Observational/ diagnostic	Detection of PIK3CA mutations in circulating free DNA in patients with breast cancer	Assessed diagnostic performance only **Tissue ARMS PCR vs plasma ARMS PCR** N=41 **Tissue ARMS PCR vs serum ARMS PCR** N=41	www.ncbi.nlm.nih.gov/pubmed/20107891	Board 2010
13	Observational/ diagnostic	Association of urinary and plasma DNA in early breast cancer patients and its links to disease relapse	Prognosis and diagnostic performance **Tissue (NR) vs ddPCR (urine)** N=200	www.ncbi.nlm.nih.gov/pubmed/29392540	Liu 2018

Abbreviations: ARMS, amplification-refractory mutation system; BEAM, beads, emulsion, amplification, magnetics; ddPCR, Droplet Digital polymerase chain reaction; DNA, deoxyribonucleic acid; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NGS, next generation sequencing; PCR, polymerase chain reaction; QP, quenching probe.

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)	Website link to research (if available)	Date
1.	Non-randomised controlled trial	Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant or Letrozole, Based on Prior Endocrine Therapy, in Patients With PIK3CA Mutation With Advanced Breast Cancer Who Have Progressed on or After Prior Treatments (BYLieve) NCT03056755	Status: Recruiting Estimated enrolment: 336 This is a phase II, multicenter, open-label, three-cohort, non-comparative study of alpelisib plus endocrine therapy (either fulvestrant or letrozole) in patients with HR+, HER2-negative aBC harboring PIK3CA mutation(s) in the tumor whose disease has progressed on or after prior treatments	clinicaltrials.gov/ct2/show/NCT03056755	Estimated primary completion date: April 2020

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    The Royal College of Pathologists of Australasia (RCPA) – **REDACTED.**

    Medical Oncology Group of Australia (MOGA) – **REDACTED.**

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    Not applicable

21. **List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    Breast Cancer Network Australia (BCNA) – **REDACTED**

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    Not applicable

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    Name of Pathologist 1: **REDACTED**

    Name of Pathologist 2: **REDACTED**

    Name of Medical Oncologist 1: **REDACTED**

    Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Worldwide, breast cancer is the most common cancer diagnosed and the leading cause of cancer-related death in women (Global Burden of Disease Cancer Collaboration 2018).[8] 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).[9] While breast cancer in men is rare, with < 1% of breast cancer diagnoses in male subjects, treatment recommendations are the same for both the genders.

Based on the expression of hormone receptors and HER2, breast cancer can be categorised into different histopathologic subtypes. Approximately 60-70% of breast tumours are HR+/HER2–.[10] 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).[11] Endocrine therapy may be given in first, second, or later lines of therapy for advanced breast cancer.[12] 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.[13] 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).[14] No predictive biomarkers have been identified to select patients that would benefit the most from these therapies to date.[15]

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[8] Global Burden of Disease Cancer Collaboration (2018) 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 Oncology 4(11): 1553-1568.

[9] breast-cancer.canceraustralia.gov.au/statistics

[10] O'Brien et al (2010) Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clin Cancer Research; 16(24): 6100-10.

[11] Cardoso et al (2017) 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC3). Breast; 31:244–259.

[12] National Cancer Center Network Treatment Guidelines for Breast Cancer, Version 2/2018. Available from: <https://www.nccn.org/store/login/login.aspx?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf> (Accessed 20-Nov-2018).

[13] Shah and Dickler (2014) Endocrine therapy for advanced breast cancer. Clin Adv Hematol Oncol; 12(4): 214-2.

[14] Baselga et al (2012) Everolimus in postmenopausal hormone receptor-positive advanced breast cancer. N Engl J Med; 366:520-9; Finn et al (2015) The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncology; 16(1):12-35; Hortobagyi et al (2016) Ribociclib as first-line therapy for HR-positive, advanced Breast Cancer. N Engl J Med; 375(18):1738-48; Dickler et al (2017) MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. Clin Cancer Res; 23(17):5218-24; Loibl et al (2017) Palbociclib combined with fulvestrant in premenopausal women with advanced breast cancer and prior progression on endocrine therapy: PALOMA-3 results. Oncologist; 22(9):1028-38; Sledge et al (2017) MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol; 35(25):2875-84.

[15] Pernas et al (2018) CDK4/6 inhibition in breast cancer: current practice and future directions. Ther Adv Med Oncol; 10:1-15; Shah and Dickler (2014) Endocrine therapy for advanced breast cancer. Clin Adv Hematol Oncol; 12(4): 214-2; Hortobagyi et al (2016) Ribociclib as first-line therapy for HR-positive, advanced Breast Cancer. N Engl J Med; 375(18):1738-48.

The phosphoinositide 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.[16] PI3K signalling is known to be a critical step in mediating the transforming potential of oncogenes and tumor suppressors in many tumor types,[17] and changes in PI3K activity are associated with resistance to endocrine, chemo-, radio-, and anti-HER2 therapies.[18] 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.

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

As noted in Question 24 above, the population comprises postmenopausal women and men with HR+/HER2– advanced breast cancer who have progressed on or after treatment with an aromatase inhibitor. Thus, patients potentially eligible for testing for a PIK3CA mutation would have had previous pathology testing for diagnosis of and characterisation of their breast cancer, and previous treatment with an aromatase inhibitor. In the SOLAR 1 trial, a majority of the PIK3CA-mutant population underwent one or more of surgery, radiotherapy and chemotherapy, REDACTED.

PIK3CA activating mutations are reported in approximately 45% of HR+/HER2– breast cancers.[19] Multiple PIK3CA hotspot mutations can be found on exons 7, 9 and 20. The SOLAR 1 trial uses the Qiagen *therascreen*® RGQ PCR tissue test (CDx) as the main evidentiary standard, 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 PIK3CA mutations targeted by the three tests are shown in Table 1 along with the prevalence of the mutations found using tissue samples. 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.

[16] Samuels et al (2004) High frequency of mutations of the PIK3CA gene in human cancers. Science; 304(5670):554; Fruman and Rommel (2014) PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov; 13(2):140-56; Zhang et al (2017) A Pan-cancer proteogenomic atlas of PI3K/AKT/mTOR pathway alterations. Cancer Cell; 31(6):820-32; Zehir et al (2017) Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med; 23(6):703-713; Janku et al (2018) Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol; 15(5):273-291.

[17] Liu et al (2009) Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov; 8:627-44.

[18] Keegan et al (2018) PI3K inhibition to overcome endocrine resistance in breast cancer. Expert Opin Invest Drugs; 27(1):1-15.

[19] Cancer Genome Atlas Network (2012) Comprehensive molecular portraits of human breast tumors. Nature; 490(7418):61-70;

Table 1 Comparison of PIK3CA mutations targeted by the two evidentiary standard tests

PIK3CA mutation	Qiagen therascreen - CDx (tissue or plasma) N=572	Roche cobas - CTA (tissue) N=395	Frequency in SOLAR 1 study population
Any	✓	✓	59.6%
Exon 7	✓	✓	*1.0%*
C420R	✓	✓	1.0%
Exon 9	✓	✓	*28.8%*
E542K	✓	✓	10.5%
E545A	✓		NR
E545D	✓		0.9%
E545G	✓		0.7%
E545K	✓		8.7%
E545X[20]		✓	11.9%
Q546E	✓		0.2%
Q546K[21]	✗		-
Q546R	✓		0.3%
Q546X[22]		✓	0.3%
Exon 20	✓	✓	*33.7%*
H1047L	✓		1.2%
H1047R	✓		13.5%
H1047Y	✓		<1%
H1047X[23]		✓	26.8%

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

Patients diagnosed with HR+/HER2– advanced breast cancer generally initially receive endocrine therapy such as tamoxifen or an aromatase inhibitor. Initial endocrine therapy may have been in the adjuvant setting, or as first-line therapy for de novo advanced breast cancer. More recently, a CDK inhibitor may be used in combination with the non-steroidal aromatase inhibitor in the advanced breast cancer setting. This is shown in the Current Clinical Pathway presented in Figure 1, Attachment A.

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

The proposed medical service is testing for PIK3CA activating mutations. Subsequent treatment would be dependent on the test result as follows:

- Patients testing positive for a PIK3CA mutation would receive treatment with alpelisib (in combination with fulvestrant)

[20] Includes E545A, D, G and K.
[21] Not included in Qiagen therascreen test. Included in Roche cobas test but only reported within Q546X.
[22] Includes Q546E, K and R.
[23] Includes H1047L, R and Y.

- Patients testing negative for a PIK3CA mutation would receive usual care (as outlined in Q38).

Eligibility

Postmenopausal women and men with HR+/HER2– advanced breast cancer who have progressed on or following treatment with an aromatase inhibitor would be eligible for testing. REDACTED.

REDACTED

Testing and treatment

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.

Novartis is planning to explore different testing scenarios (i.e. prior to second-line treatment for advanced breast cancer, and prior to first- and second-line treatment; with or without the option of plasma testing); advice on these scenarios from the Department and PASC would be welcome.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Not applicable

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Not applicable

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

The PIK3CA test is currently being carried out in a small number of laboratories in Australia; however, as similar biomarker testing is widespread it is not expected that the addition of PIK3CA testing would require any additional investment for laboratories.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

Rebiopsy may be required for some patients.

32. If applicable, advise which health professionals will primarily deliver the proposed service:

PIK3CA testing would be undertaken in pathology laboratories.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

It could not be delegated or referred to another professional for delivery.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

As noted in Question 27, surgeons, oncologists and general practitioners would order PIK3CA testing and pathology laboratories would perform the testing.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

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 Australia (RCPA).

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):

- ☐ Inpatient private hospital (admitted patient)
- ☐ Inpatient public hospital (admitted patient)
- ☐ Private outpatient clinic
- ☐ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☐ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

PIK3CA testing would take place in the pathology departments of both commercial and hospital pathology laboratories.

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

Not applicable

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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

The nominated comparator is no testing for PIK3CA activating mutations and treatment with usual care. Usual care is made up of a 'basket' of different treatment options as outlined below. The relative proportions of patients that currently receive each treatment option will be examined during the preparation of the co-dependent submission. **REDACTED**

The lines of therapy and associated treatment options are presented in the Current Clinical Pathway algorithm in Attachment A (Figure 1). **REDACTED**.

REDACTED

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

As shown in Attachment A, 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.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☐ In addition to (i.e. it is an add-on service)
☒ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

It is expected that the majority of patients who fail an aromatase inhibitor (**REDACTED**) would be tested for PIK3CA mutations to determine the most appropriate subsequent treatment (i.e. alpelisib in combination with fulvestrant or the current appropriate usual care). However, the following patient groups would likely not be considered not suitable for treatment with alpelisib (in combination with fulvestrant):

- REDACTED.

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Two Proposed Clinical Pathways are presented in Attachment A: (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.

REDACTED

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), where testing for PIK3CA mutation is included in the workup for patients with recurrent or stage IV invasive breast cancer that is HR+/HER2–, 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.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

For postmenopausal women and men with HR+/HER2– advanced breast cancer who are PIK3CA mutation positive, it is expected that treatment with alpelisib (in combination with fulvestrant) would result in superior efficacy and non-inferior safety compared with the usual care these patients would receive if they were not tested.

Postmenopausal women and men with HR+/HER2– advanced breast cancer who are PIK3CA mutation negative would receive usual care, the same treatment these patients would receive if they were not tested.

44. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

REDACTED

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Test outcomes

Rate of rebiopsy

Adverse events related to rebiopsy

Drug outcomes

Adverse events associated with subsequent treatment

Deaths

Clinical Effectiveness Outcomes:

Test outcomes

Trial-based (evidentiary standard) PIK3CA mutation analytical performance

Sensitivity

Specificity

Positive predictive value

Negative predictive value

Comparative performance of other PIK3CA mutation testing methods

Concordance

Drug outcomes

Progression-free survival

Overall survival

Response rate

Quality of life

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. **Estimate the prevalence and/or incidence of the proposed population:**

    REDACTED

47. **Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:**

    REDACTED

48. **How many years would the proposed medical service(s) be required for the patient?**

    REDACTED

49. **Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

    REDACTED

50. **Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:the projected number of patients who will utilise the proposed medical service(s) for the first full year:**

    REDACTED

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

REDACTED

52. Specify how long the proposed medical service typically takes to perform:

The time taken to perform the test will vary depending on the methodology used.

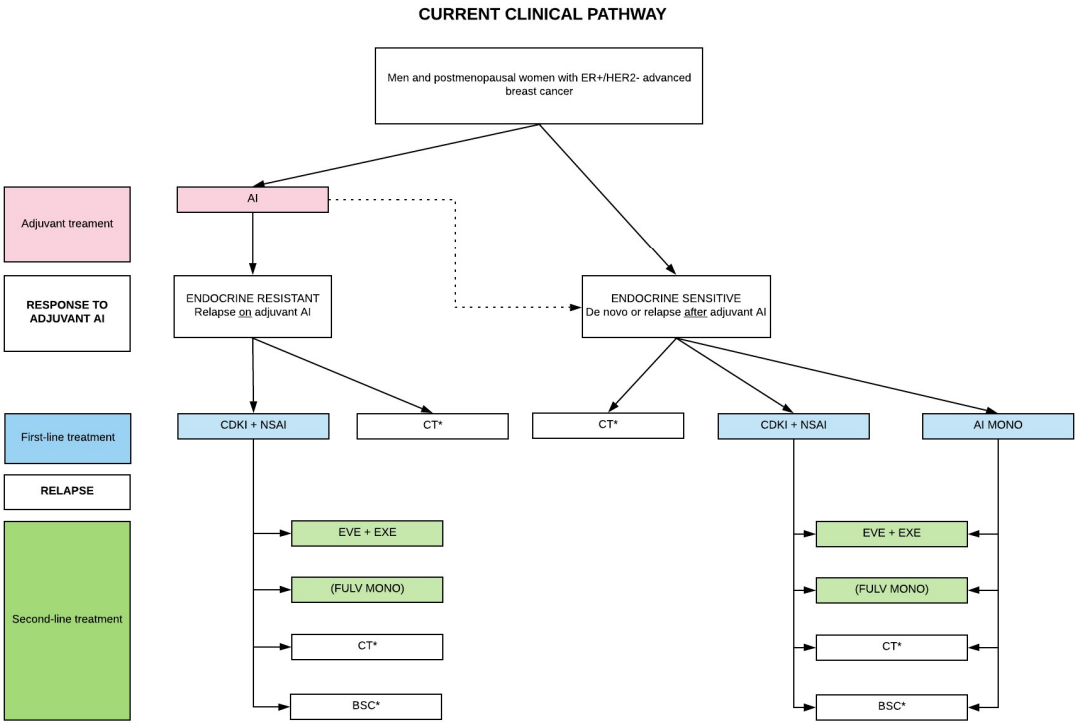
53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

The proposed descriptor may be refined depending on the outcome of feedback from PASC and discussions with the Department.

Category 6 – PATHOLOGY SERVICES
REDACTED Fee: to be determined

ATTACHMENT A

Figure 1 Current Clinical Pathway



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 2 Proposed Clinical Pathway 1 – including PIK3CA testing and treatment with alpelisib in combination with fulvestrant (second-line only)

REDACTED

Figure 3 Proposed Clinical Pathway 2 – including PIK3CA testing and treatment with alpelisib in combination with fulvestrant (first- and second-line)

REDACTED