Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1787 – Immunohistochemistry testing of solid tumour tissue to determine folate receptor alpha (FRα) expression status in adults with platinum resistant ovarian cancer to determine eligibility for Pharmaceutical Benefits Scheme (PBS)-subsidised mirvetuximab soravtansine treatment

Applicant: **Abbvie Pty Ltd**

Date of MSAC consideration: **31 July 2025**

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 requested:

- Medicare Benefits Schedule (MBS) listing of an immunohistochemistry (IHC) test of folate receptor alpha (FRα) expression in patients with high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (EOC), to determine eligibility for treatment with mirvetuximab soravtansine (MIRV); and
- Pharmaceutical Benefits Scheme (PBS) Authority Required (Streamlined) listing of MIRV for the treatment of patients with platinum-resistant high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (PROC), who have received at least one prior systemic treatment regimen, and who have high FRα tumour cell expression (defined as ≥75% of viable tumour cells with moderate (2+) or strong (3+) membrane staining [≥75%, PS2+]) as determined by a validated test.

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 deferred its advice on the public funding of immunohistochemistry (IHC) testing of solid tumour tissue to determine folate receptor alpha (FRα) expression status in adults with platinum-resistant ovarian cancer, to determine eligibility for Pharmaceutical Benefits Scheme (PBS) subsidised mirvetuximab soravtansine (MIRV, marketed as Elahere®). MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its July 2025 meeting deferred its consideration of MIRV noting the TGA delegate's overview is expected by September 2025. Additionally, MSAC noted that the PBAC was of a mind to recommend MIRV pending updates.

MSAC acknowledged there was a high clinical need for treatments for this condition. MSAC considered FRα testing would identify patients expected to benefit from MIRV and testing would have no additional safety concerns. MSAC was inclined to support the test if the PBAC recommended MIRV and the TGA approves the companion diagnostic test for FRα testing. MSAC considered the financial impact of testing to the MBS would be relatively low. MSAC considered the proposed fee of $125 for the test was high and advised a fee of $112 was appropriate.

Consumer summary
This application from AbbVie Pty Ltd requested Medicare Benefits Schedule (MBS) listing of a test to detect a protein called folate receptor alpha (FRα) that is present in ovarian cancer cells that are resistant (stops responding) to chemotherapy treatment with drugs containing platinum. People who have levels of FRα above a certain threshold would be eligible to access a medicine called mirvetuximab soravtansine (MIRV) under the Pharmaceutical Benefits Scheme (PBS). At the time this application was made, MIRV was not listed on the PBS, so a codependent application that proposed public funding for MIRV and the FRα test was submitted to the Pharmaceutical Benefits Advisory Committee (PBAC) and MSAC at the same time. In Australia, ovarian cancer is the 6th highest cause of death from cancer in women. Ovarian cancer is often diagnosed late in the disease. The 5-year survival rate of ovarian cancer is less than 50% -- meaning fewer than half of women who have ovarian cancer survive more than five years after the treatment. MSAC noted that ovarian cancer usually has a good response to initial chemotherapy treatment with drugs containing platinum, but if this treatment becomes ineffective, there are not many other options available. Ovarian cancer treatments have not improved much in over 20 years and therefore new treatment options are required. FRα is a protein that is found on the surface of many ovarian cancer cells and its levels can be tested. A test result is considered positive when the level of FRα (expression) is above a certain level (threshold). The medicine has two parts called mirvetuximab, which is an antibody that attaches to the FRα protein, that is linked to an anti-cancer component called soravtansine. Once attached to the cancer cells with FRα protein, mirvetuximab delivers the anti-cancer drug component to the cancer cell. Soravtansine then interrupts the cell's internal structure, causing the cancer cell to stop growing and die. MSAC considered that FRα testing was safe, effective and would accurately identify people who may benefit from MIRV. MSAC considered an appropriate fee for the test was $112. MSAC considered FRα testing had acceptable value for money and would have a low financial impact on the MBS. MSAC noted that the Pharmaceutical Benefits Advisory Committee (PBAC) at its July 2025 meeting deferred its advice for listing of MIRV on the PBS as MIRV had not been approved yet by the Therapeutic Goods Administration (TGA). Furthermore, PBAC was of a mind to recommend the drug to be listed on the PBS provided some updates were made. Therefore, MSAC deferred its advice but was inclined to support the FRα test if MIRV is listed on the PBS and the test is approved by the TGA. **MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing** MSAC deferred its advice but was inclined to support the public funding of IHC testing of solid tumour tissue to determine FRα expression status on the MBS for patients with ovarian cancer, to determine eligibility for PBS subsidised mirvetuximab soravtansine, if the PBAC recommends the drug mirvetuximab soravtansine and the TGA approves the test for FRα testing. MSAC considered the test was safe and it would have an acceptable financial cost to the MBS.

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

MSAC noted this integrated codependent application from AbbVie Pty Ltd sought Medicare Benefits Schedule (MBS) listing of an immunohistochemistry (IHC) test for folate receptor alpha (FRα) expression in patients with platinum-resistant ovarian cancer (PROC) to determine eligibility for treatment with Pharmaceutical Benefits Scheme (PBS)-subsidised mirvetuximab soravtansine (MIRV) of those patients who have high FRα tumour cell expression (defined as ≥75% of viable tumour cells with moderate (2+) or strong (3+) membrane staining [≥75%, PS2+]).

MSAC noted the proposed test, VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (the FOLR1 test) – the companion diagnostic assay and the codependent drug, MIRV, had not yet been approved by the Therapeutic Goods Administration (TGA). MSAC also noted a quality assurance program (QAP) is required to be implemented if the test is listed on the MBS and that the applicant has contacted the Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP) requesting a QAP be developed. Additionally, MSAC noted that the test could be offered by the laboratories in Australia as an in-house in vitro diagnostic (IVD), provided it complies with accreditation standards (National Pathology Accreditation Advisory Council [NPAAC] and National Association of Testing Authorities [NATA]).

MSAC noted that all consultation feedback received was supportive of the application.

MSAC acknowledged the high unmet clinical need for effective treatment options for patients with ovarian cancer. MSAC noted in Australia, ovarian carcinoma is the sixth leading cause of cancer-related deaths in women[1], largely due to its tendency to be diagnosed at a late stage, when treatment becomes less effective. This late presentation contributes to a high mortality rate, with a 5-year survival rate of less than 50% (Cancer Australia, 2019). While initial treatment with platinum-based chemotherapy often shows a good response, many patients experience platinum-resistant ovarian cancer (PROC). There has been little improvement in outcomes over the past 20 years, highlighting a significant unmet clinical need and new effective treatment options are urgently required.

MSAC noted that the proposed intervention was IHC testing for FRα expression status using VENTANA FOLR1 (FOLR1-2.1) test, which is the clinical utility standard and was used in the key MIRASOL and FORWARD-I trials. MSAC noted that FRα, a transmembrane protein involved in transporting folate into cells, is highly expressed in more than 35% of PROC cells[2], while being minimally expressed on normal tissue. MSAC also noted that the MIRASOL trial investigated the drug (MIRV) which is a first-in-class antibody-drug conjugate (ADC) that combines an FRα-binding antibody with a cleavable linker, and the tubulin-targeting chemotherapy agent maytansinoid DM4.

MSAC noted that FRα is an expression-based biomarker based on an endogenous gene rather than an oncogene or a variant-based biomarker, so there is a potentially weaker relationship between biomarker presence and treatment response. However, MSAC also noted the data appeared to support the predictive validity of FRα expression as a biomarker, as long as the expression level is high using ≥75%, PS2+ scoring criteria. MSAC noted that FRα testing is an IHC test with inherent interpretation challenges well understood by pathologists due to the subjective nature of assessing cell staining. MSAC also noted the applicant's pre-MSAC response emphasised that IHC testing procedures are well established in Australian pathology laboratories and the performance of FRα expression testing using the FOLR1 assay was unlikely to differ materially in Australia compared to other countries with similar laboratory accreditation standards. MSAC considered FRα testing is likely easy to interpret and advised that any discordance due to lack of reference standard and borderline results could be confirmed by a second pathologist.

MSAC noted evidence for predictive value of the FRα biomarker for MIRV treatment effect from data in MIRASOL and FORWARD-I trials which indicated high positive percent agreement, negative percent agreement, positive predictive value and negative predictive value. However, MSAC also noted there was a high risk of bias in the linked evidence approach due to the inclusion of retrospective studies in the applicant developed assessment report (ADAR). Furthermore, MSAC noted that the submission did not adequately consider the test performance, particularly for false

[1] https://www.canceraustralia.gov.au/publications-and-resources/position-statements/testing-ovarian-cancer-asymptomatic-women/background

[2] Matulonis UA, et al. Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study. *J Clin Oncol.* 2023 May 1;41(13):2436-2445. doi: 10.1200/JCO.22.01900.

positives (FPs) and false negatives (FNs). However, MSAC considered that the FRα test would be straightforward to interpret, so the risk of FPs and FNs would be low.

MSAC noted the need for ocular health management in patients receiving MIRV as there is a risk for treatment-related keratitis, and that patient education on the requirement for eye checks and available treatments was essential.

MSAC was inclined to support the following MBS item descriptor (Table 1) and agreed with the revised fee of $112 (to align with Claudin 18 IHC testing resulting from consideration of MSAC application 1767[3]) and recommended that the item should be pathologist determinable. Therefore, a practice note (i.e. PN.1.2) would be appropriate to include in the item descriptor to support the proposed MBS item descriptor.

Table 1 MBS item descriptor (MSAC inclined to support)

Category 6 – Pathology Services
MBS item XXXX A test of tumour tissue using immunohistochemistry for the detection of membrane folate receptor alpha (FRα) tumour expression status, requested by a specialist or consultant physician, if the test is: • in a patient with high-grade serous epithelial ovarian, fallopian tube or primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer; and • to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme. (See PN.1.2 of explanatory notes to this Category)
Fee: $112.00 Benefit: 75% = $84.00; 85% = $95.20

MSAC noted the comparator was no FRα biomarker testing, which was considered appropriate.

MSAC noted the proposed clinical management algorithm, in which the IHC test can be performed either at primary diagnosis of ovarian cancer or at confirmation of PROC.

Regarding safety, MSAC noted that the applicant stated that patients undergoing biopsy at primary diagnosis would not experience complications of rebiopsy. MSAC noted that the submission did not take into account the issue of insufficient archival tissue for testing that may lead to delays in treatments. MSAC noted data from the Cancer Screening Program (CaSP) registry[4] suggested the current rates of biopsy at confirmation of PROC are 11% for 2nd line treatment and 14% for 3rd line of treatment possibly due to insufficient archival tissue for testing. MSAC noted the pre-MSAC response from applicant indicated a strong preference from oncologists and pathologists for testing at primary diagnosis, alongside other IHC tests, as it would allow batch testing, thereby reducing the likelihood of testing errors and avoiding delay in treatment once platinum resistance is determined. On balance, MSAC considered that testing was safe and there would be no additional safety concerns.

MSAC noted the economic model, which was a partition survival model with 3 health states (pre-progression, post-progression and death). MSAC noted that aside from the number of tests required to identify one patient with high FRα expression and subsequent treatment with MIRV the model did not incorporate other FRα testing variables. As a result, the incremental benefits and costs of FRα testing compared with no FRα testing could not be established. MSAC further noted

[3] https://www.msac.gov.au/applications/1767

[4] Quantium analysis of CaSP data as of 23 Jan 2025

the applicant's pre-MSAC response which stated that the structure of the economic model assessing FRα testing and MIRV was consistent with some codependent submissions where the treatment outcomes are modelled in the test positive population only. MSAC agreed with the commentary that this limitation could have been addressed using sub-group data from the FORWARD-I trial. However, MSAC considered this was acceptable in the context the test being straightforward to interpret with low rates of FNs and FPs.

MSAC considered there would be negligible impact on the incremental cost effectiveness ratio (ICER) whether FRα testing occurs at primary diagnosis or at platinum resistance.

MSAC noted the financial and budgetary impacts for FRα testing either at primary diagnosis (base case) or at PROC confirmation (scenario analyses). MSAC agreed with the commentary that the number of incident patients may have been double counted, or the number of prevalent patients may have been underestimated. MSAC considered that this created uncertainty in the predicted number of patients tested at PROC confirmation and the associated costs to the MBS. MSAC also noted the revised costing provided by the department that reduced the proportion of high-grade serous ovarian cancer from 90% to 63% and calculated the cost to the MBS based on a fee of $112 instead of $125, which further reduced the costs to the MBS. MSAC noted that the cost of the IHC test – either at primary diagnosis or at PROC confirmation – was a small proportion of the overall cost to health budgets. Therefore, MSAC considered that the financial and budgetary impacts were acceptable.

MSAC noted the Pharmaceutical Benefits Advisory Committee (PBAC) at its July 2025 meeting deferred its consideration of MIRV noting the TGA delegate's overview for MIRV is expected by September 2025. Additionally, MSAC noted that the PBAC was of a mind to recommend MIRV pending regulatory updates. Therefore, MSAC was inclined to support MBS listing of IHC testing to determine FRα expression, conditional on the Australian Register of Therapeutic Goods (ARTG) listing of the test and a positive recommendation for MIRV from the PBAC. Further, MSAC reconsideration of this application may be conducted out-of-session following fulfilment of the specified requirements.

4. Background

This integrated codependent application is the first application to the MSAC for immunohistochemistry (IHC) testing of FRα expression in patients with high-grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma cancer (EOC), to determine eligibility for treatment with mirvetuximab soravtansine (MIRV).

5. Prerequisites to implementation of any funding advice

The test proposed in this submission is the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (Roche Diagnostics). The assay uses the Ventana Benchmark staining platform.

The proposed test is a qualitative IHC assay which employs a mouse antibody to FRα protein as a reagent for staining of formalin fixed paraffin embedded (FFPE) EOC patient tumour tissue sections. IHC testing is a commonly used technique in pathology laboratories. The ratified PICO Confirmation noted that laboratories should be able to use whichever Therapeutic Goods Administration (TGA) approved product they choose for the test (or use an in-house in vitro diagnostic) provided their methods meet accreditation standards (National Pathology Accreditation Advisory Council [NPAAC] and National Association of Testing Authorities [NATA]) (p18, 1787 ratified PICO Confirmation).

Both the proposed test, the VENTANA FOLR1-2.1 companion diagnostic assay (the FOLR1 test) and the medicine, MIRV, are under regulatory review by the TGA. During the evaluation, the sponsor for MIRV advised that the TGA Delegate's advice for the drug component would be available by 2

September 2025 and the outcome from the TGA Advisory Committee on Medicines (ACM) would be available by 24 October 2025.

As yet, the Ventana FOLR1 test is not on the market in Australia and FRα expression is not a routine biomarker test offered by pathology laboratories for EOC patients. A Quality Assurance Program (QAP) for IHC testing of FRα expression has been proposed, but not yet been implemented by the RCPAQAP.

PASC considered that if FRα testing is done at diagnosis, then the testing should be pathologist determinable (reflex testing) and would need to be considered to be included in the list of pathologist-determinable services (p32, 1787 ratified PICO Confirmation).

6. Proposal for public funding

The proposed MBS item descriptor for IHC testing of FRα expression in EOC patients with platinum resistance is in Table 2.

The commentary noted that there were inconsistencies in the descriptions of the test populations described in the submission. For instance, a single test population was proposed in the PICO table (Table 2) which made no reference to time of testing. However, the proposed MBS items and treatment algorithm considered two test populations which were closer to the test populations recommended by PASC (Table 5) and reflected timing of a FRα expression testing at two different points of the EOC disease course.

The descriptor for testing at confirmation of platinum resistance is in Table 2.

Table 2: Proposed MBS item descriptor: FRα expression testing at platinum-resistance

Category 6 – Pathology Services
MBS item XXXX A test of tumour tissue using immunohistochemistry for the detection of membrane FRα tumour expression, in a patient with: platinum resistant high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer As requested by a specialist or consultant physician, to determine eligibility for treatment with a relevant treatment under the Pharmaceutical Benefits Scheme (PBS).
Fee: $125.00 Benefit: 75% = $93.75; 85% = $106.25

Source: Table 1.4-4 Proposed MBS Item Descriptor: FRα Expression Testing at Platinum-resistance, p16 of the submission.
FRα= folate receptor alpha; MBS= Medical Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; TBC= to be confirmed.
Note: The PICO Confirmation noted that the PBS restriction would specify any FRα testing threshold and this need not be included in the MBS items.

The commentary considered that compared with the descriptor ratified by PASC, the proposed wording for testing at platinum resistance omitted reference to 'serous' histology, however this was included in the descriptor for testing at diagnosis (see comments below). The ratified PICO Confirmation stated that PASC, noting the evolution of understanding of platinum resistance, considered the item descriptor should not define 'platinum resistant', hence timing has not been included in the descriptor wording (between cessation of platinum treatment and onset of resistance).

In the majority of cases, testing at platinum resistance would involve retrieval of archival tumour tissue and the proposed item would be co-claimed with MBS item 72860.

The descriptor for testing at primary diagnosis of EOC is in Table 3.

Table 3: Proposed MBS item descriptor: FRα expression testing at primary diagnosis

Category 6 – Pathology Services
MBS item XXXX A test of tumour tissue using immunohistochemistry in a patient with high-grade serous epithelial ovarian, fallopian tube or primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer, requested by a specialist or consultant physician ~~or certified pathologist~~ to determine membrane FRα expression status for access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS). (See para PN.1.2 of explanatory notes to this Category)
Fee: $125.00 Benefit: 75% =$93.75; 85% = $106.25

Source: Table 1.4-3 Proposed MBS Item Descriptor: FRα Expression Testing at Diagnosis, p16 of the submission.
FRα= folate receptor alpha; MBS= Medical Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; TBC= to be confirmed.
Wording in strikethrough or underlined was amended during evaluation to reflect comments in the ratified PICO confirmation that "the item descriptor would not make reference to a 'certified pathologist' as the requestor, [but would] instead include a reference to the pathologist determinable practice note PN.1.2."
Note: The PICO Confirmation noted that the PBS restriction would specify any FRα testing threshold and this need not be included in the MBS items.

The commentary considered that the proposed item descriptor differed from the test population in the submission PICO (Table 4) in several respects:

- Inclusion of 'serous' tumour histology
- Inclusion of tumours with endometrioid, or undifferentiated histology as eligible for testing
- Inclusion of the wording 'or certified pathologist'.

The commentary also noted that regarding the first two criteria, inclusion of criteria referring to tumours of serous histology and tumours with endometrioid, or undifferentiated histology were each consistent with PASC recommendations (and therefore appropriate). Nevertheless, both criteria in the item descriptor were inconsistent with the remainder of the submission which otherwise appeared to be seeking a test and treatment population not limited to serous tumours but on the other hand without including endometrioid, or undifferentiated histology. As such, the commentary considered the proposed differences in the item descriptors compared with those in the ratified PICO Confirmation were not adequately justified. The submission proposed that FRα expression testing performed as a reflex test at the time of the primary diagnosis and as such would be a pathologist determinable service. The inclusion of the wording 'or certified pathologist' (Table 3) reflected this intent, thus the reference in the descriptor is indicated in strikethrough type. The item descriptor was amended during evaluation (wording in strikethrough or underlined) to reflect comments in the ratified PICO confirmation that "the item descriptor would not make reference to a 'certified pathologist' as the requestor, [but would] instead include a reference to the pathologist determinable practice note PN.1.2.".

The commentary considered that the proposed MBS services would be limited to pathology laboratories with NATA accreditation for this type of testing and enrolled in a QAP for this assay (see above comments in Prerequisites to implementation).

The commentary noted that the submission proposed a fee of $125 for both items but did not provide a supporting justification in the ADAR as requested by PASC (p31 1787 ratified PICO Confirmation, PASC December 2024).

The key PICO components presented in the submission are presented in Table 4.

Table 4: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Patients with high-grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma cancer Drug: Patients with platinum-resistant high-grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma cancer. Patient must have high FRα expression, defined as ≥ 75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining
Intervention	Test: Qualitative IHC assay for assessment of FRα protein expression in tumour tissue Drug: Mirvetuximab soravtansine
Comparator	Test: No testing for FRα expression levels *Reference standard [a]: None* Drug: • Non-platinum chemotherapy (paclitaxel, topotecan or pegylated liposomal doxorubicin) • Non-platinum chemotherapy plus bevacizumab
Outcomes	Test: Prognostic effect, diagnostic performance, clinical utility, safety Drug: OS, PFS, objective response rate, rates and nature of adverse events, and QoL measures
Clinical Utility Standard	Ventana FOLR1 (FOLR1-2.1) RxDX Assay
Clinical claim	Test: In patients with high grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma cancer, FRα testing is superior to no testing to identify patients suitable for MIRV treatment. Drug: In patients with high grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma cancer, with FRα high expression identified by IHC, MIRV is more effective than ICC and no testing at improving OS.

Source: Adapted from Table 1.1-2 Key Components of the Clinical Issue Addressed by the Codependent Submission, pp5-6 of the submission.
FRα= folate-receptor alpha; ICC= investigator's choice of chemotherapy; IHC= immunohistochemistry; MIRV= mirvetuximab soravtansine; OS= overall survival; PFS= progression-free survival; QoL= quality of life.
[a] *although not included in the source table, the lack of an applicable reference standard for this test is stated elsewhere in the submission.*

The submission proposed two MBS descriptors with test populations different to that in Table 4 above, reflecting the timing of tests at two different points of the EOC disease course (testing at primary diagnosis and testing at platinum resistance).

The commentary noted that compared with the treatment population in the ratified PICO Confirmation, the requested wording captured a broader population, omitting the following criteria:

- Serous histology
- Prior treatment with no more than three lines of previous systemic therapy
- Testing by a validated assay

The commentary noted that the submission's PICO table was therefore not consistent with the PICO recommended by the PICO Advisory Subcommittee (PASC), shown in Table 5 (1787 ratified PICO Confirmation, PASC December 2024).

Table 5: PICO elements as recommended in the ratified PICO Confirmation

Component	Description
Population	<u>Test</u> *If performed at confirmation of platinum resistance:* Adult patients with platinum resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer. *If performed at primary diagnosis of ovarian cancer:* Adult patients with high-grade serous epithelial ovarian, fallopian tube, primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer. <u>Treatment</u> Platinum resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer whose tumour have a high level of folate receptor alpha (FRα) expression according to the PS2+ scoring method (i.e. ≥75% of viable tumour cells with moderate [2+] or strong [3+] staining) as determined by a validated immunohistochemistry (IHC) assay and which has been treated with no more than three lines of previous systemic therapy.
Prior tests	If performed at confirmation of platinum resistance: Test(s) to confirm high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer.

Component	Description
	If performed at primary diagnosis of ovarian cancer: Test(s) to confirm diagnosis of high-grade serous epithelial ovarian, fallopian tube, primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer.
Intervention	Test IHC testing on solid tumour tissue to determine FRα expression based on prevalence in terms of percentage of viable tumour cells and level in terms of intensity of staining. Treatment Mirvetuximab soravtansine.
Comparator/s	Test No testing for FRα expression levels. Treatment Standard of care: non-platinum treatment (paclitaxel, topotecan, or pegylated liposomal doxorubicin) and supportive care with or without bevacizumab.
Reference standard	None.
Clinical utility standard	VENTANA FOLR1 (FOLR1-2.1) RxDx Assay to determine FRα expression levels.
Outcomes	Test Safety outcomes: adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing. Diagnostic performance: intra- and inter-reader variability; test failure rate; evidence of stability of proteins in archival tissue; heterogeneity within the same tissue sample; evidence of stability in FRα status over time with treatment and/or progression of disease; test-retest reliability. Clinical utility of the test: determine whether testing for FRα predicts variation in the treatment effect of mirvetuximab soravtansine in terms of health outcomes for patients. Qualitative assessment of potential risks associated with an incorrect test result or incorrect interpretation of results. Failure of the test to perform as expected or failure to correctly interpret test results may lead to improper patient management decisions. Drug Safety outcomes: Safety and tolerability of treatment with mirvetuximab soravtansine compared to alternative treatments assessed by adverse events, physical examination, laboratory findings and vital signs. Clinical effectiveness outcomes: objective response rate (ORR) overall survival (OS) progression-free survival (PFS) health-related quality of life (HRQoL). Healthcare system outcomes: cost of testing per patient and cost associated with re-biopsies (e.g.: early-stage disease that has relapsed, test failure, inadequate sampling) cost of treatment and cost of treating adverse events financial implications: number of patients tested; number of patients treated.
Assessment questions	What is the safety, effectiveness, cost-effectiveness and total costs of FRα expression level testing and treatment with mirvetuximab soravtansine versus no testing and standard of care, in platinum resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer? Does testing for FRα predict a treatment effect modification with mirvetuximab soravtansine? What are the potential costs and cost offsets associated with disease management arising from the listing of FRα testing?

Source: Table 1, 1787 ratified PICO Confirmation, PASC December 2024.
FRα: folate receptor alpha; HRQoL: health-related quality of life; IHC: immunohistochemistry; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PS2+: scoring of moderate [2+] or strong [3+] staining; RxDx: registered diagnostic test.

The commentary considered that the submission addressed most of the PICO elements relating to the proposed test, as prespecified in the PICO confirmation that was ratified by PASC. Data from the key FORWARD-I trial representing test negative patients were only partially presented in the submission. The submission did not present an assessment of diagnostic accuracy for the proposed test, taking into account the prevalence-adjusted estimates of test performance.

7. Population

Epithelial ovarian, fallopian tube, and primary peritoneal cancer are collectively described as EOC. There are currently no recommended screening tests for ovarian cancer, and the absence of definitive symptoms makes it difficult to diagnose in the early stages (Cancer Australia, 2019). Late-stage EOC is rarely curable despite optimal surgical resection and intensive adjuvant or neo-adjuvant chemotherapy. Due to the ambiguous nature of typical EOC disease symptoms, a lack of early detection tests, and because early-stage disease is typically asymptomatic, 70% of patients receive a late-stage diagnosis (stage III-IV) (Cancer Council, 2024).

At the time of diagnosis, women have a five-year survival rate of 48% (Australian Cancer Research Foundation [ACRF], 2022). Ovarian cancer was ranked 6th highest as a cause of cancer death in Australian women in 2022 (Cancer Australia, 2024; NCCI, 2022). For Australian patients with advanced or metastatic EOC with serous histology, a median overall survival (OS) of 5.2 years was reported for a cohort of 421 women, in an unpublished draft study commissioned for this submission (registry data collected by the not-for-profit Cancer Screening Program [CaSP]) (Quantium, 2025).

Ovarian cancer is managed according to tumour histology. Figure MSAC.1 is presented to conceptualise the currently understood spectrum of tumour subtypes, differentiated according to histology, and their proportions.

Figure MSAC.1 Diagram of ovarian cancer subtypes by histology

Epithelial ovarian cancer (EOC)	**85-90%**	**Serous**	**70-75%**	**High grade**	**95-97%**
				Low grade	3-5%
		Clear cell carcinoma (5-12%) Endometrioid (11-20%) Mucinous (3%) Others (mixed; undifferentiated <5%)	25-30%		
Non-epithelial OC (stromal or germ cell)	10-15%				

Source: Developed during the evaluation from Section 1.1.3.1. Disease Background (p5-7 of the submission); Redi et al, (2017); González-Martín et al, (2023); Bergstrom et al, (2017) (cited in the MIRASOL CSR); Fleury et al, (2015); Atallah et al, (2023) (cited in the 1787 PICO Confirmation).
EOC= epithelial ovarian cancer; OC= ovarian cancer.

The PICO Confirmation noted feedback from the sponsor's clinical experts that testing at primary diagnosis should include patients with high-grade endometrioid, or undifferentiated EOC as these histological subtypes can be difficult to distinguish from high-grade serous EOC.

The proposed test population was a single population of patients with high-grade epithelial ovarian, fallopian tube or primary peritoneal carcinoma cancer. The commentary noted that this differed from the two test populations recommended in the ratified PICO Confirmation, either testing at primary diagnosis or testing on diagnosis of platinum resistance. The submission's proposed treatment algorithm and MBS items however did identify the two separate test populations. The submission's test population which was indicated in PICO table, management algorithm and MBS item descriptors omitted the following criteria specified by the PASC (Table 1, 1787 ratified PICO Confirmation):

- For testing at primary diagnosis only: additional histological subtypes "high grade endometrioid or undifferentiated EOC".
- For testing at platinum resistance (MBS items) or both populations (management algorithm): A limitation to serous histology.

The Commentary noted differences between the proposed test population(s) in the submission PICO (Table 5), the proposed management algorithm, and the MBS items were not explained by the submission and could not be resolved.

The biomarker applicable to this submission is the FRα protein. The scoring criteria for the proposed IHC test and its application to determine patient eligibility for MIRV through the PBS are defined in Table 6.

Table 6: FRα Expression Scoring Criteria (Ventana FOLR1 Dx)

IHC interpretation	Staining description	Proposed to be eligible for MIRV
Positive for FRα* (high FRα)	≥ 75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining	Yes
Negative for FRα*	< 75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining	No
Not evaluable	Artifacts making interpretation not possible	No

Source: Table 1.1-8 FRα Expression Scoring Criteria, p18 of the submission
Dx= device; FRα = folate receptor high alpha; FOLR1= folate receptor alpha: MIRV= mirvetuximab soravtansine.
* To decrease variability of results for cases with percentage of tumour cells near the threshold of 75% (65% to 85%), re-reading of the slide by a second pathologist is recommended. The case result with percentage of tumour cells between 65-85% by a pathologist should be adjudicated by one or two independent pathologists. The patient's final result with regard to FOLR1 Positive should be obtained by either a majority rule or by consensus among the pathologists.

The scoring defined in the United States (US) product information (PI) specifies membrane staining of 2 or 3, described as PS2+. At least 75% of a minimum 100 viable tumour cells counted must fulfill the PS2+ criteria in Table 6 for the test result to be considered positive. The commentary noted that no draft Instructions for Use (IFU) for Australia was provided in the submission for the Ventana FOLR1 Dx assay.

The submission presented evidence to show that patients with higher FRα expression did better than those with lower expression when treated with MIRV (see discussion of FORWARD-I trial results), but no quantitative evaluation of expression levels or titration of this effect was undertaken to identify to the actual threshold of treatment effect (for example, no receiver operating characteristic [ROC] curve). The use of a threshold for positivity has resulted in FRα status being treated as a binary variable with no testing of alternative thresholds, such as 70% or 85%.

The submission defined the biomarker prevalence (FRα high expression) in the target population based on results of the Phase II SORAYA trial which reported a rate of 36% of PROC patients with FRα high expression (Matulonis et al, 2023). This differs from the US Food and Drug Administration (FDA) Summary of Safety and Effectiveness report for the proposed test (Ventana FOLR1 assay) (FDA 2022) which cited a rate of 28.75% positive based on analysis of a commercial cohort of EOC resected tissue samples (N=953). The US test PI states that borderline results should be adjudicated by a second independent pathologist thus the final value for prevalence of high FRα expression among EOC patients may include a portion of the borderline values. The commentary considered that the submission's value of 36%, which is higher than the FDA estimate, may be plausible as an upper bound.

The submission cited results from a sub-study of the MIRV Phase I trial, which tested archived tissue samples from 27 patients and compared results with pre-treatment and post-treatment tissue (Martin et al, 2017) (Table 7)

Table 7: Re-testing of archival tissue and testing of fresh biopsy (Martin et al, 2017)

	Archival tissue	Pre-treatment biopsy	Post-treatment (Cycle 2, Day 8)
Sufficient sample / tumour cells	N=27	N=21	N=17
Met FRα positivity threshold on re-testing ≥25% (PS2+)	27/27 (100%)	15/21 (71%)	10/17 (59%)

Source: compiled during the evaluation from pp141-142 of the submission and Martin et al, (2017).
FRα= folate receptor alpha; PS2+= FRα membrane staining at moderate (2) or high (3) intensity.

The submission argued that 'high concordance' of FRα expression in evaluable pre-treatment biopsies versus archival tumour samples, suggesting that archival tissue can be reliably used to identify patients with receptor-positive tumours, specifically with respect to pre-specified thresholds of FRα expression. The commentary considered this conclusion may not be reasonable

given the authors reported decreasing concordance between archival tissue (collected at diagnosis), pre-treatment samples (71%) and samples post-treatment with MIRV (59%) (Table 7), noting that these were based on small patient numbers. This appears to suggest that there is uncertainty relating to the stability of the biomarker over time. The commentary noted at the time this finding was not investigated further in any subsequent MIRV trials.

The commentary noted that all patients in the key MIRASOL and FORWARD-I trials were tested for FRα expression as part of trial screening (that is, at platinum resistance). The clinical study reports (CSRs) for both trials reported that where possible, archival tissue was used for testing though biopsy was undertaken in cases where archival tissue was insufficient. Numbers of patients in whom a biopsy was required versus those whose archival tissue was used were not reported for either trial in the submission. Data extracted from the MIRASOL listings indicated only 2 of the 453 patients in the trial underwent a biopsy for FRα expression testing.

8. Comparator

The test comparator was 'no testing'. In a test agnostic population, PROC patients currently receive standard of care treatment (non-platinum chemotherapy with or without bevacizumab).

For the assessment of test performance in the linked evidence approach, there was no reference standard. Hence, the commentary employed measures of positive percent agreement (PPA) and negative percent agreement (NPA) from concordance studies to inform test performance in place of sensitivity and specificity (according to the MSAC Guidelines).

9. Summary of public consultation input

Consultation input was welcomed from:

1787 – Immunohistochemistry testing of solid tumour tissue to determine folate receptor alpha (FRα) expression status in adults with platinum-resistant ovarian cancer, to determine eligibility for treatment with PBS subsidised mirvetuximab soravtansine (Abbvie Pty Ltd)	**No. of Inputs Received**
Organisations (2)	
I am providing input on behalf of a consumer group or organisation. Consumer organisations are not-for-profit organisations representing the interests of healthcare consumers, their families and carers.	2
Grand Total	**2**

The organisations that submitted input were:

- Rare Cancers Australia (RCA) **(2)**
- Ovarian Cancer Australia (OCA)

Level of support for public funding

Both RCA and OCA expressed support for the public funding of this application.

Comments on PICO

- RCA noted the proposed eligibility criteria appears relevant, but suggested the criteria should consider including patients with earlier signs of platinum-resistance or other related biomarkers, as they may also benefit from such targeted interventions.
- OCA noted the proposed eligibility criteria as appropriate in this setting, capturing an accurate representation of those who may benefit most from this testing. OCA stated that utilising FRα levels to help determine eligibility for treatment with the FRα antibody drug conjugate,

mirvetuximab soravtansine (MIRV), will help ensure the drug is considered for use only on those who are more likely to benefit.
- RCA noted further clarity is needed to ensure that the study population aligns with the real-world patient demographics in Australia, including any variances in genetic markers or health statuses that might affect treatment outcomes, and advocated for pan-tumour approval pathways.
- OCA noted the ovarian cancer community needs options for those who do not fit into current recommended treatment pathways, whilst also ensuring that resourcing is used accordingly and the appropriate patients who may benefit most from these therapies are identified.

Perceived Advantages

- RCA noted the proposed testing will provide access to a more targeted, effective treatment for platinum-resistant ovarian cancer, potentially slowing disease progression and improving quality of life. RCA also noted the ability to identify suitable treatments based on FRα status offers patients a sense of agency and clearer treatment pathways.
- OCA noted that enabling funded-testing for FRα to determine eligibility for MIRV will provide much needed and long-awaited hope for those diagnosed with platinum-resistant epithelial ovarian cancer. OCA also noted available treatments are very limited and are not selected based on any type molecular testing, and highlighted this test has the potential to have meaningful impacts on patients in identifying a treatment that is targeted and therefore has a better chance of working as proven by clinical trials.

Perceived Disadvantages

- OCA noted a potential barrier of this test is where it is incorporated into clinical pathways, in order to ensure optimal care is delivered to all patients who may be eligible for this test and subsequent therapy. OCA highlighted that to avoid any barriers to successful implementation, consideration should be given to the timing in the treatment and diagnosis pathway of this test.

Support for Implementation and Issues

- RCA noted barriers to successful implementation include geographic disparities in testing access, potential gaps in healthcare provider awareness, and cost implications for uninsured services.
- RCA noted the proposed delivery as suitable, but stated considerations required to ensure equitable access, including:
    - Ensuring that FRα testing is available across Australia, including in rural and remote areas, will be essential. Integrating the testing process with local pathology services could reduce the need for travel and improve access.
    - Additional support services, such as counselling and pain management, should be included to address the complex needs of patients undergoing immunohistochemistry testing and subsequent treatments.
- RCA also recommended setting an affordable MBS fee that does not place an undue burden on patients, as well as providing transparent information about any potential out-of-pocket costs.
- OCA noted consideration must be undertaken for the appropriate point in the disease pathway that this testing is recommended and performed. OCA stated that while testing for FRα upfront at the time of diagnosis may result in testing for those who won't go on to require MIRV, consideration should be given to whether the timing of this test alongside other diagnostics might reduce the risk of women falling through the cracks when they are later determined to be platinum-resistant.

- OCA noted that with tumour testing at recurrence not currently standard of care in ovarian cancer management, decisions on the timing and systems of this test usage and reimbursement must support equitable access to optimal care, including for priority populations. However, OCA described the FRα immunohistochemistry test as a well-established testing method in Australian laboratories, with no significant challenges expected in actual test delivery.

10. Characteristics of the evidence base

A summary of the studies and trials in the linked evidence approach is shown in Table 8, specific areas where evidence was lacking are outlined in Table 9. The commentary noted that none of the test outcomes reported in the studies were used in the economic model.

Table 8: Summary of the linked evidence approach

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	James et al, (2024) Retrospective analysis of pathology samples from MIRV Phase II trial (SORAYA) used to establish concordance in use of the clinical utility standard in different settings Martin et al (2017) sub-study to the MIRV Phase I trial; testing of archived tissue vs fresh pre-treatment biopsy vs fresh post-treatment biopsy FDA (2022) evaluation report for Ventana FOLR1 assay; reports results of James et al, (2024); includes results of separate biomarker prevalence study (N=953)	☒ k=3 n=100+24+28+438 (based on multiple test performance analyses) n=27 n=953	James et al, (2024) and Martin et al, (2017) high RoB due to lack of reference standard. FDA (2022) – RoB not applicable.
Prognostic evidence (longitudinal accuracy)	Four non-comparative observational studies Lawson et al (2024) Köbel et al (2014) Crane et al (2012) Kalli et al (2008)	☒ k=4 n=251 n=2801 n=361 n=213	High
Change in patient management	No evidence presented	☐ k=0 n=0	--
Health outcomes (clinical utility)	No evidence presented *(i.e. no studies of all patients tested, both biomarker positive and negative)*	☐ k=0 n=0	--
Predictive effect (treatment effect variation)	Comparison of outcomes in the whole trial population (stratified according to FRα expression) vs FRα-high subgroup, both groups receive either MIRV or ICC. Exploratory analysis of FRα-high vs FRα-medium (latter is effectively test negative) according to previously used test scoring criteria. Post hoc analysis of re-scored patients in FRα-low, medium and high groups according to test scoring criteria proposed for the submission.	☒ k=2 n=366 n=148 FRα medium n=218 FRα high (based on 10X scoring)	FORWARD-I Low RoB for prespecified outcomes High RoB for post hoc analysis
Treatment effect (enriched)	Single RCT of MIRV vs ICC in patients that are FRα-high (test positive) in both arms	☒ k=1 n=453	MIRASOL – high RoB
Other	Single RCT of bevacizumab + ICC versus ICC as indirect evidence for the bevacizumab + ICC comparator	☒ k=1 n=361	AURELIA – high RoB

Source: compiled during the evaluation.
ICC= investigator's choice of chemotherapy; FDA= Food and Drug Administration; FRα= folate receptor alpha; k= number of studies, MIRV= mirvetuximab soravtansine; n= number of patients; RCT= randomised control trial; RoB= risk of bias.

Table 9: Data availability to inform comparisons

Proposed test vs no test	No evidence presented	
Proposed test vs alternative test	No evidence presented	
Concordance	Test performance of the FRα test clinical utility standard as used in the MIRV trials and also in practice, based on concordance of results in different settings (intermediate precision and reproducibility) proposed to be representative of the test once implemented in Australia (James et al, 2024; FDA 2022)	
Expression stability	Martin et al, (2017) comparison of FRα expression at 3 time points.	
	MIRV	**ICC; bevacizumab + ICC[a]**
Biomarker test positive	MIRASOL	MIRASOL; AURELIA
Biomarker test negative	Partially applicable: FORWARD-I FRα-medium subgroup	Partially applicable: FORWARD-I FRα-medium subgroup

Source: compiled during the evaluation.
ICC= investigator's choice of chemotherapy; FDA= Food and Drug Administration; FRα= folate receptor alpha; k: number of studies, MIRV= mirvetuximab soravtansine.
[a] the comparator bevacizumab + ICC is only studied in the AURELIA trial.

The commentary noted there was no evidence presented in the ADAR for:

- Investigation of MIRV versus standard of care (investigators choice of chemotherapy [ICC]) in the biomarker negative population as defined by the proposed ≥75% FRα expression cutoff and PS2+ staining.
- Performance of the test in Australia
- Change in clinical management

The submission presented direct evidence of MIRV versus ICC in the target patient population of FRα-high expression (biomarker positive) EOC patients who have been diagnosed as platinum resistant (MIRASOL). An indirect comparison with a third trial (AURELIA) provided indirect evidence of MIRV versus bevacizumab +ICC based on the common comparator of ICC (biomarker agnostic population) (not discussed further with respect to the test).

The commentary noted that the MIRV program did not explicitly examine treatment effect in test negative patients. However, the direct evidence was supported by a trial in a broader population (FORWARD-I) comparing MIRV versus ICC which included a subgroup of FRα-medium expression patients who would be defined as test negative according to the submission. The trial employed a previously used definition of FRα biomarker positivity (≥50% expression cutoff) and scoring method. No evidence in biomarker negative patients using the proposed definition (≥75% expression cutoff) and scoring criteria was available for this submission. Hence, the commentary considered that the submission used a linked evidence approach to support the use of the MIRV / FRα-high expression test combination.

The linked evidence approach included additional studies of the biomarker and test performance. Studies presented in the submission for test performance are summarised in Table 10. The commentary noted that these were all retrospective non-comparative cohort studies at high risk of bias.

Table 10: Overview of Characteristics of Included Studies: test performance and accuracy of FRα IHC

Study ID	Risk of bias	Study type	Population, N	FRα positivity definition	FRα method	Outcomes
James et al (2024)	High[a]	Retrospective study	SORAYA Phase II trial EOC test samples Inter-reader precision: N=100 Intra-reader precision: N=100 Intermediate precision/ repeatability: N=24 External reproducibility: N=28 Test failure: N=438	PS2+ (≥75% of cells stained)	Ventana FOLR1 assay	PPA, NPA, OPA; intra-and inter-reader precision, test-retest reliability, test failure
Previs et al (2024)	High[a]	Retrospective study	Pathology cases Total EOC N=425 High grade serous n/N=199/425 (46.8%)	According to instructions: PS2+ (≥75% of cells stained)	Ventana FOLR1 assay	Stability of FRα in archival tissue, stability in FRα status over time
Martin et al (2017)	High[a]	Retrospective study cases enrolled in MIRV Phase 1 expansion cohort study	EOC patients N=27 Of which archive tissue available, n/N=21/27	≥25% of tumour staining at ≥2+ intensity	Ventana FOLR1 assay	Concordance study FRα expression in archival tissue vs fresh biopsy
Kalli et al (2008)	High[a]	Retrospective study of ovarian pathology cases	OC cases[b]: Total N=213 (%) Primary n/N=186/213 (87.3) Serous n/N=104/186 (55.9) Recurrent n/N=27 (12.7) Serous n/N=22/27 (81.5)	Any staining was positive. Reported by quartiles: >75% +ve 51%-75% +ve 26%-50% +ve <25% +ve	In-house IHC using FBP343 antibody[5] for FRα staining	Stability in FRα status over time
FDA, 2022	Not applicable	Regulatory evaluation of nonclinical and clinical data	(no single study – data supplied by sponsor)	(evaluation of sponsor proposal)	(no single study – data supplied by sponsor)	Sensitivity[b]; specificity[c]; precision; reproducibility; tissue heterogeneity

Source: adapted from Table 2.9-8 Overview of Characteristics of Included Studies: Test Performance and Accuracy, p132 of the submission.
EOC=epithelial ovarian cancer; FRα= folate receptor alpha; IHC= immunohistochemistry; n= number of events; N= number of patients; NPA= negative percent agreement; OC= ovarian cancer; OPA= overall percent agreement; PPA= positive percent agreement.
a The absence of a reference standard in these studies conferred a high risk of bias according to the QUADAS-2 tool.
b Sensitivity was examined using a panel of EOC tissue samples without comparison to a reference (no rates of true or false positives were reported).
c Specificity was examined with a qualitative method only to check assay antibody specificity for FOLR1 c.f. FOLR2 and FOLR3 proteins. No detection rates, true or false negatives were reported.

A summary of the four included studies reporting on the potential prognostic effect of FRα expression is provided in Table 11.

[5] Franklin WA, et al. New anti-lung-cancer antibody cluster 12 reacts with human folate receptors present on adenocarcinoma. *Inter J Cancer*. 1994;57(S8):89-95.

Table 11: Overview of characteristics of included studies: Prognostic effect of FRα expression

Study ID	Risk of Bias[a]	Site (date range)	Population, *N*	*FRα positivity definition*	FRα method	Outcomes
Lawson et al (2024)	*High*	MD Anderson Cancer Centre (Houston, TX) (Jan 2023 – 1 Oct 2023)	Gynaecologic cases: *Total N=215* *High-grade serous n/N=162/215 (75%)*	*PS2+ (≥75% of cells stained)*	*Ventana FRα IHC (antibody clone FOLR1-2.1)*	OS, PFS
Köbel et al (2014)	*Unclear*	Enrolled in 12 studies part of OTTA consortium (see footnote [b])	OC cases: *Total N=2801* *High grade serous n/N=1507/2801 (53.8%)*	*FRα negative is absent / weak staining.* *FRα positive is all others:* *Strong: 1-50% cells stained* *Strong membranous: >50%* *Strong cytoplasmic: 50-95%* *Strong cytoplasmic: >95%*	*In-house IHC using BN3.2 antibody (Novocastra) for FRα staining*	OS, PFS
Crane et al (2012)	*High*	University Medical Centre Groningen (Netherlands) *(1985 – 2002)*	OC cases: *Total N=361* *Serous n/N=201/361 (55.7%)* *Non-serous n/N=116/361* *Missing n/N=35/361*	*According to method of Bagnoli et al, (2003)[6] using ≥25% threshold* *0 = no staining; 1 = weak staining; 2 = moderate staining; 3 = strong staining.*	*In-house IHC using mAB343 antibody (Endocyte) for FRα staining*	OS, PFS
Kalli et al (2008)	*High*	Mayo Clinic (Rochester, MN) (Jun 1991 – Jun 2005)	OC cases[c]: *Total N=213* *Primary n/N=186/213 (87.3%)* *Serous n/N=104/186 (55.9%)* *Recurrent n/N=27 (12.7%)* *Serous n/N=22/27 (81.5%)*	*Any staining was positive. Staining reported by quartiles >75% positive; 51%-75% positive; 26%-50% positive; <25% positive*	*In-house IHC using FBP343 antibody[7] for FRα staining*	OS, RFS

Source: Adapted from Table 2.8-4 Overview of Characteristics of Included Studies: Prognostic Effect of FRα Expression, p112 of the submission.

FRα= folate receptor alpha; IHC= immunohistochemistry; n= number of events; N= number of patients; OC= ovarian cancer; OS= overall survival; OTTA= Ovarian Tumour Tissue Analysis; PFS= progression-free survival; QUIPS Quality In Prognosis Studies tool; PS2+= FRα membrane staining at moderate (2) or high (3) intensity; RFS= recurrence-free survival.

a Risk of Bias assessment using the Quality In Prognosis Studies (QUIPS) tool.

b OTTA consortium Included studies undertaken in: Australia (2002 to 2006); Canada, (1998 to 2009); Germany (2002 to 2006); Canada (2003 to 2007); United States (2003 to 2009); Denmark (1994 to 1999); United States (2000 to 2009); United Kingdom (1998 to 2008); Canada (1995 to 2003); United Kingdom (2006 to 2010) and Canada (1984 to 2000).

c Kalli et al, (2008) excluded borderline carcinoma and non-epithelial malignancies from the study.

Text added during the evaluation is in italics.

11. Comparative safety

Adverse events from testing

The submission argued that FRα expression testing at primary diagnosis would be performed as part of diagnostic work-up and would not confer any additional safety risks. Testing of tumour FRα expression at the time of platinum-resistance would also confer no additional safety risks if tumour tissue retrieved from archive storage was adequate.

If tissue was unavailable or inadequate for testing at platinum resistance, a fresh biopsy would be indicated. The submission presented two retrospective studies reporting safety outcomes in women being investigated for ovarian masses (Griffin et al, 2009 [N=60]; Thabet et al, 2014

[6] Bagnoli M, et al. A step further in understanding the biology of the folate receptor in ovarian carcinoma. *Gynecol Oncol.* 2003 Jan 1;88(1):S140-4.

[7] Franklin WA, et al. New anti-lung-cancer antibody cluster 12 reacts with human folate receptors present on adenocarcinoma. *Int J Cancer*. 1994;57(S8):89-95.

[N=27]) to support its conclusion that there were no material safety concerns associated with biopsy procedures in patients with ovarian cancers.

The commentary considered this was not reasonable. Complications associated with minimally invasive gynaecological procedures such as biopsies are well recognised to include bleeding, infection, perforation, pain, extension of hospitalisation, re-investigations and, rarely, other events such as sepsis and thromboses. The two cited studies (Griffin et al, 2009 [N=60]; Thabet et al, 2014 [N=27]) were likely too small to be powered for less common complications of minimally invasive surgery and were restricted to one type of biopsy procedure. Other studies have reported moderate blood loss in 4.5% of ultrasound-guided biopsies (Verschuere et al, 2021[8] [N=155]) and Grade 2 events (pain or haematoma) in 2.5% of image-guided biopsies (Goranova et al, 2017[9] [N=202]). Larger studies would likely detect other less commonly observed events. Although incidence of these events are low, potential risks are considered to be inherently part of the biopsy procedure.

Furthermore, the commentary noted that the rates of biopsy reported in the CaSP registry data for PROC patients (11% in second line and 14% in third line) were considered applicable to the test population of patients at platinum resistance due to possibly insufficient archival tissue for testing.

Adverse events from changes in management

The submission did not provide any data for test failure or false results for the requested test in Australia as the proposed Ventana FOLR1 assay (or in-house alternative) has not yet been implemented for routine use in Australian laboratories.

Data for test performance from concordance testing were described for the clinical utility standard (see Table 12 below). The commentary considered that although the submission did not present estimates of prevalence adjusted positive predictive value (PPV) or negative predictive value (NPV), these were calculated during the evaluation using both the submission's assumptions of performance and biomarker prevalence (PPV 96.4% [95% CI 94.6, 97.7]; NPV 97.92% [95% CI 97.2, 98.5]) and the evaluator's assumptions (PPV 85.1% [95% CI 81.9, 87.8]; NPV 97.15% [95% CI 96.4, 97.7]). Based on calculations conducted during the evaluation (and assuming the Ventana FOLR1 assay performs in Australia the same as in the MIRV clinical program), testing of the target patient population in Australia would result in:

- Approximately 15 false negatives for every 100 patients tested. These patients would likely receive standard of care (non-platinum chemotherapy with or without bevacizumab) instead of MIRV and receive some treatment benefit.
- Approximately 3 false positives for every 100 patients tested. These patients would receive inappropriate MIRV treatment. Based on the survival outcomes for FRα medium expression subgroup in the FORWARD-I study, these patients would experience minimal treatment benefit from MIRV and do worse than if they had received non-platinum chemotherapy.

The clinical performance of FRα expression testing used in the context of identifying patients eligible for enrolment in the MIRV SORAYA trial was reported by James et al, (2024). The intent to diagnose (ITD) population consisted of all screened patients for the SORAYA trial for whom at least one sample was tested and FRα expression was tested using the Ventana FOLR1 assay (N=438). Of the ITD population, 431 (98.4%) patients had an FRα expression result. The complement of this analysis represents the test failure rate, that is 7/438 (1.6%) of tumour specimens did not have

[8] Verschuere H, et al. Safety and efficiency of performing transvaginal ultrasound-guided tru-cut biopsy for pelvic masses. *Gynecol Oncol*. 2021 Jun 1;161(3):845-51.
[9] Goranova Tet al. Safety and utility of image-guided research biopsies in relapsed high-grade serous ovarian carcinoma—experience of the BriTROC consortium. *Br J Cancer*. 2017 May;116(10):1294-301.

evaluable FRα status after testing. According to the authors, test failure was based on staining acceptability, assuming slide tissue morphology was acceptable.

Equivalent test failure results were not reported in the submission or in CSRs for the FORWARD-I or MIRASOL trials.

The commentary noted that these events were not incorporated in the submission's economic model. Only test positive patients were included in the trial population. No results of patient screening that indicated test performance were included in the data received for review.

12. Comparative effectiveness

Effectiveness (based on linked evidence)

Evidence for predictive value of the FRα biomarker for MIRV treatment effect was restricted to the MIRV trials. The submission presented MIRASOL (the FRα high expression population based on the PS2+ scoring criteria) and FORWARD-I (the FRα medium and high expression populations based on the 10X scoring criteria). The available trials and the comparison they inform are summarised above in and , respectively.

The submission included two key clinical trials – MIRASOL and FORWARD-I – intended to examine biomarker positive patients only. However, the nominated threshold for FRα positivity of the FORWARD-I was redefined post-hoc to be a minimum 75% of positively stained tumour cells (the scoring criteria were also revised at the same time). Therefore, the FRα-medium patients in the FORWARD-I trial (defined as 50% to <75% expression according to 10X scoring) would be considered biomarker negative based on the requested test criteria for the submission. The commentary considered that for the purpose of examining treatment response and the predictive value of the biomarker, the FRα-medium patients were considered an adequate subset of the test negative population for this evaluation.

Data for test performance in the Australian context was absent. The submission assumed that the Ventana FOLR1 assay, once implemented in Australian laboratories, will have the same performance as the clinical utility standard employed in the MIRV clinical trials.

FRα expression testing, scoring criteria and thresholds for positive results used in the MIRV trials are summarised in Table 12.

Table 12: FRα assays and scoring used during MIRV development

Study ID	Staining	Assay [a] Antibody clone	Laboratory	Cells counted	Threshold for positivity	Patients included
Phase I[c]	Minimum level 2 (moderate) or level 3 (strong) ("PS2+") membrane staining intensity	Dose escalation[b]: Leica FRα IHC assay NCL-L-FRalpha BN3.2 Expansion cohort: Ventana robust prototype assay FOLR-2.1-clone 353.2.1	Expansion: Single central laboratory	Minimum 100 viable tumour cells	Low: 25%<50% cells Medium: 50%-74% cells High: ≥75% cells	Minimum ≥25% FRα Low, medium or high FRα expression
SORAYA (Phase II)	Minimum level 2 (moderate) or level 3 (strong) ("PS2+") membrane staining intensity	Ventana FOLR1 Assay Clone FOLR1-2.1	2 Histo-GeneX (now CellCarta) central laboratories	Minimum 100 viable tumour cells	High: ≥ 75% cells	High FRα expression only
FORWARD I	Any cells with visible staining at 10X magnification (any intensity)	Ventana FOLR1 Assay Clone FOLR1-2.1	Single central laboratory	Minimum 100 viable tumour cells	Medium: 50%-74% cells High: ≥75% cells	Medium or high FRα expression
MIRASOL	Minimum level 2 (moderate) or level 3 (strong) ("PS2+") membrane staining intensity	Ventana FOLR1 Assay Clone FOLR1-2.1	3 central laboratories	Minimum 100 viable tumour cells	High: ≥ 75% cells	High FRα expression only

Source: Compiled for this evaluation from: Elahere European Public Assessment Report, 19 September 2024 (EMEA/H/C/005036/0000); Martin et al, (2017); James et al, (2024).

FRα= folate-receptor alpha; IHC= immunohistochemistry; MIRV= mirvetuximab soravtansine; PS2+= FRα membrane staining at moderate (2) or high (3) intensity.

[a] Development assay information from European Public Assessment Report, 19 September 2024 (EMEA/H/C/005036/0000) (p124).

[b] The Ventana robust prototype assay was also used to retrospectively re-test samples from the initial dose escalation phase.

[c] Testing for entry to the Phase I study was based on archival samples only.

Comparative accuracy/test performance

A summary of the diagnostic accuracy of the clinical utility standard is given in Table 13, including prevalence adjusted estimates, the number needed to test (NNT) to identify one positive patient, and the number needed to yield one misdiagnosed patient.

Table 13: Diagnostic accuracy of the FRα clinical utility standard based on concordance

Positive percent agreement (PPA)	
Submission (analysis of James et al, 2024)	96.3% (95% CI 93.6, 97.9)
James et al, (2024); FDA (2022)	93.2% (95% CI 89.4, 96.8)
Negative percent agreement (NPA)	
Submission (analysis of James et al, 2024)	98.0% (95% CI 95.7, 99.1)
James et al, (2024); FDA (2022)	93.4% (95% CI 89.9, 96.8)
EOC biomarker prevalence estimate	
Submission (MIRV program)[a]	36% (NR)
FDA (2022)	28.75% (NR)
[Estimated] Prevalence-adjusted PPV for use of the test in Australia[b]	
Based on the submission	96.4% (95% CI 94.6, 97.7)
Based on the evaluation	*85.1% (95% CI 81.9, 87.8)*
[Estimated] Prevalence-adjusted NPV for use of the test in Australia[b]	
Based on the submission	97.92% (95% CI 97.2, 98.5)
Based on the evaluation	*97.15% (95% CI 96.4, 97.7)*
[Estimated] Number needed to test (NNT) to identify one positive patient in Australia	
Based on the submission	1.06 patients
Based on the evaluation	*1.22 patients*
[Estimated] Number needed to misdiagnose (NNM) one patient in Australia	
Based on the submission	38.28 patients
Based on the evaluation	*15.02 patients*

Source: compiled during the evaluation.
CI= confidence interval; EOC=epithelial ovarian cancer; FDA= Food and Drug Administration; NPV= negative predictive value; NR: not reported; PPV= positive predictive value.
a The submission cites MIRV study publications Moore et al, 2023; Matulonis et al 2023 for this value.
b CIs have been derived during the evaluation using the percentages without a true sample size for PPV and NPV.
All '[estimated]' values were calculated during the evaluation. Values calculated 'based on the evaluation' (i.e. using revised PPA, NPA and prevalence figures) are in italics.

The submission presented test performance information for the clinical utility standard, the Ventana FOLR1 assay. One key study by James et al, (2024) presented a summary of the clinical utility standard assay development, which was supported by the evaluation report for the test from the FDA (FDA, 2022) (which also included a small amount of additional unpublished data). The study by James et al, (2024) and the FDA evaluation (FDA, 2022) described a concordance study which reported percent agreement based on pairwise comparison among three pathologists which was the source of test performance outcomes.

The submission presented different values for PPA and NPA compared to James et al, (2024) (also cited in the FDA evaluation report). The PPA and NPA values used in the evaluation were taken from the latter (see Table 13).

The submission did not adequately consider test performance with regard to false positives or false negatives. The commentary considered that based on the prevalence-adjusted PPV and NPV calculated during the evaluation (Table 13) and assuming that the Ventana FOLR1 assay performs in Australia the same as in the MIRV clinical program, testing of the target population in Australia would result in approximately 15 false negatives and approximately 3 false positives for every 100 patients tested.

The James et al, (2024) study also reported results of an inter-laboratory reproducibility study, showing site-to-site variability of the Ventana FOLR1 assay performance (Table 14).

Table 14: Inter-laboratory reproducibility (pairwise comparison) (James et al, 2024*)

	Outcome	n/N (N=1680 reads before pairwise comparison)	% (95% CI)
Inter-site	PPA	27990/33362	83.9 (77.5, 89.1)
	NPA	28386/33758	84.1 (79.7, 88.4)
	OPA	28188/33560	84.0 (78.7, 88.7)
Inter-reader	PPA	2134/2505	85.2 (79.5, 89.9)
	NPA	2158/2529	85.3 (81.2, 89.4)
	OPA	2146/2517	85.3 (80.5, 89.6)
Inter-day	PPA	3088/3337	92.5 (89.5, 95.1)
	NPA	3126/3375	92.6 (90.5, 94.8)
	OPA	3107/3356	92.6 (90.1, 94.9)

Source: Figure 4, James et al (2024); Table1 6, Table 17, FDA (2022) .
CI= confidence interval; n= number of events; N= number of patients; NPA= negative percent agreement; OPA= overall percent agreement; PPA= positive percent agreement.
* Studies reported in James et al (2024), supplemented with additional data for same analyses evaluated in FDA (2022).
The authors described the pairwise analysis thus: "The inter-site analysis was calculated by pooling all results from all possible pairs of observations per case between sites (28 cases x 16 reader pairs per day between any 2 sites x 25 day pairs x 3 site pairs). The inter-reader analysis was calculated by pooling all results from all possible pairs of observations per case within each day at each site (28 cases x 6 reader pairs x 5 days x 3 sites)". The FDA (2022) report included additional analyses for inter-day reproducibility as part of the same dataset that were not reported in the James et al (2024) article.

The commentary considered that there is no evidence of reliability of the requested test in Australia as neither the proposed Ventana FOLR1 assay nor any equivalent in-house tests of FRα expression have been implemented for routine use, so it is unknown if test performance will vary site-to-site similarly to the values in Table 14. The requirement for NATA accreditation and enrolment in an RCPA QAP for any laboratory wishing to offer an MBS-funded FRα IHC test should mitigate variability between laboratories. Additionally, as discussed in Section 5, the commentary considered that there is uncertainty relating to the stability of the biomarker over time.

Prognostic evidence

The submission presented information on prognostic effect based on a comparison of outcomes for the untreated/standard of care population informed by retrospective testing of patient biomarker positive and biomarker negative status.

An overview of the four included studies reporting on the potential prognostic effect of FRα expression is provided above in Table 11. All four studies were retrospective non-comparative, observational studies of gynaecological IHC pathology cases. The included studies for prognostic validity were also single arm, non-comparative studies considered to be at a high risk of bias due to selection bias (Crane et al, 2012; Kalli et al, 2008) or confounding (Lawson et al, 2024; 22.4% of patients received MIRV prior to outcome reporting). Only Lawson et al, (2024) used a validated test for FRα expression IHC. Three of the four included studies Köbel et al (2014), Crane et al, (2012) and Kalli et al, (2008) employed different FRα expression test methods and as such definitions of test positivity/negativity were different to those obtained with the Ventana FOLR1 assay (which was used in the Lawson et al, 2024 study).

The commentary considered that noting the above constraints on the data, none of the four studies reported a difference in survival outcomes for the patients who tested FRα expression positive compared with FRα expression negative. As such, the commentary considered there was no evidence to suggest that FRα expression levels were informative as a prognostic biomarker for ovarian cancer.

Predictive evidence

In the MIRV Phase I study (Martin et al, 2017), 27 patients evaluable for efficacy were included in an analysis of the clinical activity of MIRV by FRα expression level (Table 15).

Table 15: MIRV treatment Effect by FRα Expression: Phase 1 Study

FRα expression	Definition	# patients	CR	PR	ORR, N (%)	PFS (months), median (95% CI)
Overall	≥25% of tumour cell with ≥2+ staining	27	2	4	6 (22.2%)	4.2 (2.8, 5.4)
Low	25%-49% of tumour cell with ≥2+ staining	6	0	0	0 (0%)	2.8 (1.3, 5.4)
Medium	50%-74% of tumour cell with ≥2+ staining	5	0	1	1 (20%)	3.9 (2.6, 12.7)
High	≥75% of tumour cell with ≥2+ staining	16	2	3	5 (31.3%)	5.4 (2.8, --)

Source: Table 2.9-24 Treatment Effect by FRα Expression: Phase 1 Study, p152 of the submission
CI= confidence interval; CR= complete response; FRα= folate receptor alpha; MIRV= mirvetuximab soravtansine; N= number of patients in cohort; ORR= objective response rate; PFS= progression-free survival; PR= partial response.

No patients with low FRα expression showed response to treatment. An increase in the percentage of patients responding to treatment, as well as median progression free survival (PFS), was reported with increasing levels of FRα expression, particularly in the FRα high expression subgroup. This formed the proof of concept for further hypothesis testing in the MIRV clinical program.

The commentary noted that the FORWARD-I trial employed a different definition of FRα expression test positivity than used for MIRASOL (and proposed for the PBS restriction for MIRV). Nevertheless, the trial supports clinical utility of the biomarker, in that it shows the rationale behind the choice of cutoff for the eligible patient population and offers a subgroup that represents a biomarker negative population.

The sponsor explored the FORWARD-I data by re-scoring the tissue samples used to determine FRα expression status in the trial using the PS2+ method and compared them to the simplified 10X method used as the basis for the trial (Table 16).

Table 16: Results of re-scoring FORWARD-I patients FRα expression levels (N=332)[a]

FRα expression Level	Cutoff	10X, N	%	PS2+, N	%	Outcome of re-scoring
FRα-low (<50%)	**0<50%**	**0**	**--**	**114**	**34%**	**Below intended expression cutoff for the FORWARD-I trial**
FRα-medium	50<75%	134	40%	20[a] 82[a]	31%	Intended expression level FRα-medium
FRα-high	≥75%	198	60%	116	35%	Intended expression level FRα-high

Source: Data extracted from slide 11 FORWARD I 10X SCORING COMPARED WITH EXPLORATORY PS2+ SCORING, Moore et al, (2019).
FRα= folate receptor alpha; N= number of patients in cohort; PS2+= FRα membrane staining at moderate (2) or high (3) intensity.
[a] Analysis population for whom samples were available; percentages indicated are of the total N=332.
[b] Values for the re-scored medium group (20+82=102) were derived during the evaluation from the numbers presented in the source document which gave a value of n=103. Investigation of these discrepancies was considered unlikely to change the resulting proportions. Shading was added to indicate the origin of the values in the re-scored groups. Light green shading indicated patients originally classified as FRα-medium and dark green shading indicated patients originally scored as FRα-high. Hatched indicated a mix of both.

Of the FORWARD-I patients originally scored as FRα-medium, 114 (85%) were re-scored as FRα-low and 20 (15%) remained as FRα-medium according to the PS2+ method. Of the group originally scored as FRα-high, 82 (41%) were rescored as medium and 116 (59%) remained as FRα-high. Therefore, according to definition of FRα test positivity requested in the submission, all the patients in the FORWARD-I FRα-medium group would have been defined as test negative and just over half (59%) of the patients in the FRα-high group would have been defined as test positive. The re-scored groups formed the basis of the post hoc analyses.

The results from the analysis of PFS by blinded independent central review (BICR) in the FORWARD-I trial are summarised in Table 17 , including the re-analysed FRα expression groups based on the post hoc analysis (low, medium and high by PS2+ scoring as per Table 17).

Table 17: FORWARD-I: analysis of PFS by BICR (February 2019 data cutoff)

Outcome	n/N with event (%)	Median time to PFS event (mo) (95% CI)	n/N with event (%)	Median time to PFS event (mo) (95% CI)	Difference in median	P-value (log rank test)	HR (95% CI)
PFS – Whole trial population							
	MIRV (N=248)		ICC (N=118)				
ITT	174/248 (70%)	4.14 (3.75, 4.53)	70/118 (59%)	4.44 (2.83, 5.59)	-0.3	0.897	0.981 (0.734, 1.310)
PFS – FRα-high (≥75%, using 10X scoring) (pre-specified)							
	MIRV (N=147)		ICC (N=71)				
FRα-high	93/147 (63%)	4.76 (4.11, 5.68)	45/71 (63%)	3.25 (1.97, 5.59)	1.51	0.049	0.693 (0.480, 1.000)
PFS – FRα-medium (<75%, using 10X scoring) (pre-specified)							
	MIRV (N=248)		*ICC (N=118)*				
FRα-medium	*81/101 (80%)*	*2.92 (2.76, 4.14)*	*25/46 (54%)*	*5.55 (2.73, 8.34)*	*-2.63*	*0.061*	*1.560 (0.976, 2.492)*
PFS – FRα expression groups (≥75%, using PS2+ scoring) (post-hoc)							
	MIRV		*ICC*				
FRα-high	50/82 (61%)	5.62 (4.04, 7.06)	25/34 (74%)	3.22 (1.51, 5.49)	2.4	0.0151	0.549 (0.336, 0.897)
FRα-medium	53/69 (77%)	4.30 (4.11, 5.59)	22/34 (65%)	5.55 (1.61, 9.10)	-1.25	0.9543	1.015 (0.611, 1.687)
FRα-low	57/76 (75%)	3.75 (2.83, 4.14)	21/38 (55%)	5.49 (1.97, 6.97)	-1.74	0.1425	1.458 (0.878, 2.420)

Source: Compiled during the evaluation from the below sources:
Table 9 Primary and secondary endpoint results for the ITT population and the FRα- high population, p18 of submission Appendix A;
Table 21: Progression-free Survival per BIRC – ITT Population, pp97-99, FORWARD-I CSR February 2019 data cutoff;
Table 22: Progression-free Survival per BIRC – FRα-high Population, pp100-102, FORWARD-I CSR February 2019 data cutoff;
Table 10 Post hoc analysis of FORWARD I: primary and secondary endpoints results for the FRα- high, FRα- medium and FRα- low population, p19 of submission Appendix A.
Table 14.2.1.1.3: Progression Free Survival BIRC - FR A Medium Level ITT Population, p662, FORWARD-I CSR.
Slides 12; 14, FORWARD I 10X SCORING COMPARED WITH EXPLORATORY PS2+ SCORING, Moore et al, (2019).
Table 65, Table 66 and Table 67, pp1-6 of Corrected Attachment 2.7 to the submission.
BICR= blinded independent central review; CI= confidence interval; CSR= clinical study report; FRα= folate receptor alpha; HR= hazard ratio; ICC= investigator's choice of chemotherapy; ITT= intention to treat analysis; MIRV= mirvetuximab soravtansine; mo= months; PFS= progression-free survival; PS2+= FRα membrane staining at moderate (2) or high (3) intensity.
Values in italics were extracted from the CSRs during the evaluation.

The primary endpoint of PFS by BICR did not meet statistical significance in either the ITT (whole trial) population or FRα-high expression (≥75%, using 10X scoring) subgroup. The median PFS for the FRα-medium population showed a pronounced lack of benefit, in which MIRV patients did worse than the ICC patients (a difference of -2.63 months median time to progression or death). The hazard ratio (HR) point estimate was above 1.0 with wide confidence intervals (1.560 [95% CI 0.976, 2.492] p=0.061).

The post-hoc re-scored subgroups showed a benefit only for the FRα-high expression group (≥75%, using PS2+ scoring) (HR 0.549 [95% CI 0.336, 0.897] p=0.0151) – this formed the basis for the hypothesis tested in the MIRASOL trial.

The results for OS in the FORWARD-I trial are summarised in Table 18. The submission presented OS results for the pre-specified subgroups from three analyses (February 2019; August 2019; March 2020). The post hoc analysis of the re-scored low, medium and high FRα expression groups was based on February 2019 data.

Table 18: FORWARD-I: analysis of OS (February 2019 and March 2020 data cutoffs)

	MIRV (N=248)		ICC (N=118)				
Outcome	**n/N with event (%)**	**Median time to event (mo) (95% CI)**	**n/N with event (%)**	**Median time to event (mo) (95% CI)**	**Difference in median**	**P-value (log rank test)**	**HR (95% CI)**
OS – Whole trial population							
	MIRV (N=248)		**ICC (N=118)**				
ITT February 2019	96/248 (39%)	16.4 (12.81, NC)	50/118 (42%)	14.0 (11.01, NC)	2.4	0.248	0.815 (0.575, 1.154)
ITT August 2019 exploratory analysis	96/248 (39%)	15.6 (NR)	50/118 (42%)	13.9 (NR)	1.7	0.278	0.846 (0.625, 1.145)
ITT March 2020	152/248](61%)	15.57 (12.85, 18.04)	75/118 (64%)	13.93 (11.40, 18.50)	1.64	0.276	0.855 (0.644, 1.134)
OS – FRα-high (≥75%, using 10X scoring) (pre-specified)							
	MIRV (N=147)		**ICC (N=71)**				
FRα-high February 2019	50/147 (34%)	NC (12.58, NC)	33/71 (46%)	11.76 (9.20, NC)	NC	0.033	0.618 (0.395, 0.966)
ITT August 2019 exploratory analysis	50/147 (34%)	16.4 (NR)	33/71 (46%)	12.0 (NR)	4.4	0.048	0.678 (0.460, 0.999)
FRα-high March 2020	82/147 (56%)	17.31 (12.81, 20.50)	45/71 (63%)	12.02 (9.20, 18.07)	5.29	0.063	0.706 (0.489, 1.020)
OS – FRα-medium (<75%, using 10X scoring) (pre-specified)							
	MIRV (N=101)		**ICC (N=46)**				
FRα-medium February 2019	*46/101 (46)*	*14.36 (12.06, 20.50)*	*17/46 (37)*	*15.18 (11.43, ---)*	*-0.82*	*0.521*	*1.203 (0.683, 2.120)*
FRα-medium March 2020	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
OS – FRα- expression groups (≥75%, using PS2+ scoring) (post-hoc)							
FRα-high	34/82 (41%)	16.43 (11.27, -)	17/34 (50%)	13.47 (6.11, -)	3.0	0.187	0.675 (0.375, 1.214)
FRα-medium	27/69 (39%)	14.23 (12.16, -)	13/34 (38%)	NC (11.76, -)	NC	0.7637	1.108 (0.569, 2.156)
FRα-low	30/76 (39%)	16.99 (12.25, -)	18/38 (47%)	11.43 (8.28, -)	5.6	0.2357	0.702 (0.390, 1.263)

Source: compiled during the evaluation from the below sources:
Table 9 Primary and secondary endpoint results for the ITT population and the FRα- high population, p18 of submission Appendix A;
Table 10 Post hoc analysis of FORWARD I: primary and secondary endpoints results for the FRα- high, FRα- medium and FRα- low population, p19 of submission Appendix A;
Table 25: Overall Survival – ITT Population, pp106-107, FORWARD-I CSR,
Table 26: Overall Survival – FRα-high Population, pp109-110, FORWARD-I CSR.
Table 1: Overall Survival – ITT Population, pp2917-2919, FORWARD-I CSR addendum;
Table 2: Overall Survival – FRα-high Population, pp2920-2921, FORWARD-I CSR addendum.
Table 14.2.3.3: Overall Survival - FR A Medium Level ITT Population, p712, FORWARD-I CSR
Slide 9, 12 FORWARD I 10X SCORING COMPARED WITH EXPLORATORY PS2+ SCORING, Moore et al, (2019).
Table 65, Table 66 and Table 67, pp1-6 of Corrected Attachment 2.7 to the submission.
BICR= blinded independent central review; CI= confidence interval; CSR= clinical study report; FRα= folate receptor alpha; HR= hazard ratio; ICC= investigator's choice of chemotherapy; ITT= intention to treat analysis; MIRV= mirvetuximab soravtansine; mo= months; NC= not calculated; NR= not reported (in the FORWARD-I CSR); OS= overall survival; PFS= progression-free survival.
Note: the conference presentation (Moore 2019) (slides 13-14) which presented the FORWARD-I post hoc analysis did not match the submission OS values for the HRs or the K-M plot and appeared to have been results from a different data cutoff.
Values in italics were extracted from the CSRs during the evaluation.

The difference in OS for MIRV versus ICC for the pre-specified FRα-high expression group was not statistically significant for the three analyses presented. For the re-scored FRα-high expression group, the median OS was 16.4 months in the MIRV arm versus 13.5 months in the ICC arm, but the results were not statistically significant (HR=0.675, p=0.187).

The predictive value of FRα level on the primary endpoint of PFS from FORWARD-I was examined by comparing outcomes for the pre-specified FRα-high and FRα-medium subgroups (Table 19).

Table 19: Predictive value of FRα level on PFS per BICR – ITT Population (December 2019 data)

	MIRV			ICC			
Type of Analysis FRα Level	**N**	**Events (%)**	**Median (95% CI) (Months)**	**N**	**Events (%)**	**Median (95% CI) (Months)**	**HR (95% CI)**
FRα-high[a]	147	93 (63)	4.8 (4.11, 5.68)	71	45 (63)	3.3 (1.97, 5.59)	0.69 (0.48, 0.98)
FRα-medium[a]	101	81 (80)	2.9 (2.76, 4.14)	46	25 (54)	5.6 (2.73, 8.34)	1.56 (0.99, 2.45)
Interaction[b]							**0.4 (0.24, 0.76) p=0.004**

Source: Table 32: Predictive Value of FRα Level on Progression-free Survival per BIRC – ITT Population, p117, FORWARD-I CSR.
BICR= blinded independent central review; CI= confidence interval; FRα= folate receptor alpha; HR= hazard ratio; ICC= investigator's choice of chemotherapy; ITT= intent to treat; MIRV= mirvetuximab soravtansine; N=number of subjects; PFS= progression-free survival.
[a] Hazard ratio is MIRV to ICC within each subgroup (high or medium). A hazard ratio < 1 indicates a reduction in hazard rate in favour of MIRV.
[b] Hazard ratio is for interaction between treatment group and FRα subgroup.

Change in management in practice

The submission did not present any clinical evidence to inform change in clinical management. FRα expression testing and treatment options targeting this biomarker are new to the EOC treatment algorithm. The published literature regarding use in practice is limited to clinical trial results. The MIRV clinical trials enrolled only biomarker positive patients which limits examination of FRα negative patients. Overall, the commentary considered that no definitive conclusions could be drawn regarding the likely change in management once FRα testing becomes available.

Claim of codependence

The commentary noted that the FORWARD-I trial results showed a difference in outcomes between the whole trial population and the FRα-high (≥75% using the PS2+ scoring method i.e. ≥75% of viable tumour cells with moderate [2+] or strong [3+] staining) subgroup, however the clearest difference was observed on comparison of the FRα-high and FRα-medium (from 50% to <75%, using the PS2+ method) subgroups. For PFS, the prespecified analyses gave HRs for FRα-high of 0.693 (95% CI 0.480, 1.000) (p=0.049) versus 1.560 (95% CI 0.976, 2.492) (p=0.061) for FRα-medium Table 17. The HR for the FRα-high group, though not statistically significant, was described in the CSR as 'a clinically meaningful advantage'. The FRα-medium group, in comparison, indicated patients on MIRV did worse than those receiving ICC. Values for OS were similar (Table 18). A test for interaction based on a comparison of the PFS results was statistically significant (p-value = 0.004) (Table 19). The FRα-high and FRα-medium groups would have each contained patients of similar performance status and prognosis, thus it was considered likely that this treatment effect was related to the FRα expression level. Given the lack of treatment response to MIRV in the FRα-medium subgroup (and the absence of data from patients either unselected for or lacking FRα tumour expression) the evaluation considered this group as a test negative population. This appeared to support the predictive validity of FRα expression as a biomarker as long as the expression level is high using the PS2+ scoring criteria. The ESCs considered FRα expression is critical to identifying patients likely to benefit from MIRV, given the potential for patients without high FRα expression to have worse survival outcomes when treated with MIRV compared to ICC, and in the context of specific safety concerns for MIRV.

The commentary considered that the numerical threshold chosen to define high FRα expression was less well supported. The FRα biomarker is an expression-based biomarker based on an endogenous gene rather than an oncogene or a variant-based biomarker. The commentary noted that the submission presented no exploration of the choice of expression ranges used for the low,

medium and high FRα expression groups for the post hoc analysis. Only limited data from the FRα-medium subgroup were provided in the submission. No analysis employing (for example) a hierarchical summary receiver operating characteristic (HSROC) curve was presented in the submission (comparing true positive rate versus false positive rate to identify a cutoff value; as indicated in the MSAC Guidelines for such circumstances).

The commentary also considered that the chosen threshold of ≥75% FRα expression was based on an assumption that FRα levels remained constant over the EOC disease course which may not be reasonable based on re-testing of archival tissue and testing of fresh biopsy (Martin et al, 2017). The ESCs noted there was limited evidence demonstrating the stability of FRα in archived formalin-fixed paraffin-embedded (FFPE) tissue blocks or tissue microarrays (TMAs) and the stability of FRα expression in disease progression or treatment. However, the ESCs noted recently reported data at a conference[10] that showed high consistency (86%) of FRα IHC status across biopsies taken at different times. The ESCs suggested further research was needed to determine the reliability of archival tissue versus fresh biopsies for FRα IHC testing.

13. Economic evaluation

The submission presented a modelled economic evaluation comparing MIRV to a mixed comparator (weighted 50:50) of ICC (based on direct evidence from MIRASOL) and BEVA + ICC (based on the indirect treatment comparison using evidence from MIRASOL and AURELIA) in a population of patients with PROC who have received at least one prior systemic treatment regimen and have high (≥ 75% of tumour cells) FRα expression. The type of economic evaluation was a cost-utility analysis.

Table 20: Summary of model structure, key inputs and rationale for economic evaluation

Component	Summary
Comparison modelled	MIRV vs mixed comparator ICC (50%) and BEVA + ICC (50%) in patients with high FRα expression (≥ 75% of tumour cells). The commentary noted that submission did not include any test outcomes in the economic model; this was not consistent with PBAC guidelines which state that, for a co-dependent technology, the model structure should capture patients at the point of testing such that the incremental benefits and costs are included for those who are both positive and negative for the test.
Time horizon	10 years in the model base case vs 13.1 months in the MIRASOL trial and 13.0 months in the BEVA + ICC arm in the AURELIA trial (median follow-up). The commentary considered that this was consistent with previous PBAC considerations for treatments for ovarian cancer. However, patients with platinum-resistant ovarian cancer have a worse-prognosis than those who are platinum-sensitive – as such, a 7.5-year time horizon (explored in a sensitivity analysis) may be a more appropriate estimate.
Outcomes	LYG, QALYs. *This was appropriate*
Methods used to generate results	Partition survival analysis. Results reported on the basis of average expected costs and consequences per patient. The commentary considered that this was consistent with economic evaluations in the literature for similar patient populations.
Health states	Pre-progression, Post-progression and Death. The commentary considered that this was consistent with economic evaluations in the literature for similar patient populations.
Cycle length	1 week. A half-cycle correction was applied to account for any transitions or events that occurred midcycle. The commentary considered that this was appropriate.
Test parameters	The submission stated that as there is no reference standard for FRα expression testing, outcomes of sensitivity and specificity and the flow-on outcomes of positive and negative predictive values are not applicable for inclusion in the model. The commentary considered that this was consistent with the ratified PICO which stated that "PASC agreed with the nominated outcomes for the test with the exception of 'sensitivity and specificity' (and by extension, the positive and negative predictive values and likelihood ratios) on the basis there is no reference standard to compare the specified test against" (p. 22, 1787 Ratified PICO Confirmation, December 2024 PASC meeting).

[10] https://meetings.asco.org/abstracts-presentations/253565

Component	Summary
Allocation to health states	MIRV and ICC: The transitioning of patients is based on independent parametric survival models fitted to PFS and OS data reported in the MIRV and chemotherapy arms of MIRASOL. The commentary considered that this was appropriate. BEVA + ICC: The transitioning of patients is based on hazard ratios (derived from the MAIC for MIRV vs BEVA + ICC) applied to the PFS and OS parametric survival models for MIRV (derived from the MIRASOL trial as described above). The commentary noted that there are concerns regarding the validity of the MAIC due to issues with the exchangeability of the trials used in the comparison to support the proposed clinical claim of superiority.
Extrapolation method	MIRV and ICC: independent parametric models fitted to each treatment arm with Log-logistic selected in base case for OS (and Log-normal for PFS) for MIRV and Weibull selected in base case for OS (and Log-normal for PFS) for ICC, based on goodness of fit (AIC/BIC) and visual inspection. BEVA + ICC: OS and PFS curves are based on the application of HRs derived from the MAIC of MIRV vs BEVA + ICC For OS and PFS, convergence was not assumed to occur within the modelled time horizon. 88% of QALYs, 93% of LYG and 18% of incremental costs (vs ICC) and 85% of QALYs, 88% of LYG and 14% of incremental costs (vs BEVA + ICC) occur in the extrapolated period. The commentary noted that the choice of parametric survival models for the base case were reasonable, except for the Log-logistic model for OS for MIRV, which ranked second best fit per AIC/BIC statistics but was deemed by the submission to be a better fit over the observed period (based on visual assessment) than the gamma survival model (best fit based on AIC/BIC statistics). Use of the Log-logistic model resulted in an estimated 4% of patients in the MIRV arm remaining alive at the end of the model time-horizon (10 years), while use of the gamma model results in no patients remaining alive after approximately 7.8 years; given the poor prognosis of patients with PROC, the use of the gamma model would be a more appropriate (conservative) choice.
Health related quality of life	Treatment-dependent utility values for the pre-progression (MIRV = 0.753, ICC = 0.736) and post-progression (MIRV = 0.681, ICC = 0.629) health states, derived from EQ-5D-5L data (UK value set) from the MIRASOL trial. Utility values for the BEVA + ICC arm assumed to be the same as ICC from MIRASOL. Pooled utility values for the pre-progression (=0.747) and post-progression (=0.657) health states were explored in a sensitivity analysis. The commentary noted that utility values applied in the economic model could not be verified by the evaluation. Further, given there was declining EQ-5D-5L completion rates through the MIRASOL trial (67%/58% at week 8/9 and 27.8%/16.8% at week 24 for MIRV and ICC respectively), the use of a pooled utility value for the post-progression health state would be more appropriate.

Source: Table 3.1-1, pp162-163 and Table 3.5-2, p186 of the submission.
AIC= Akaike Information Criterion; BEVA= bevacizumab; BIC=Bayesian Information Criterion; EQ-5D-5L= EuroQoL 5-Dimension 5-Level; FRα= Folate receptor alpha; HR= hazard ratio; ICC= investigators choice of chemotherapy; LYG= life years gained; MAIC= matching-adjusted indirect comparison; MIRV= mirvetuximab soravtansine; OS= overall survival; PBAC= Pharmaceutical Benefit Advisory Committee; PASC=PICO Confirmation Advisory Sub-Committee; PFS= progression-free survival; PROC= platinum-resistant ovarian cancer; QALY= quality-adjusted life years.

The economic model was structured as a partition survival model comprising of three discrete health states: pre-progression, post-progression and death. However, the model structure did not incorporate any FRα expression testing parameters. The submission justified the exclusion of test variables by stating that there is no reference standard for FRα expression testing, therefore outcomes of sensitivity and specificity and the flow-on outcomes of positive and negative predictive values are not applicable. The submission stated that this was consistent with the ratified PICO which outlined that "PASC agreed with the nominated outcomes for the test, with the exception of 'sensitivity and specificity' (and by extension, the positive and negative predictive values and likelihood ratios) on the basis there is no reference standard to compare the specified test against" (p. 22, 1787 Ratified PICO Confirmation, December 2024 PASC meeting). However, the commentary considered this was not consistent with MSAC guidelines which state that, for a codependent technology, the model structure should capture patients at the point of testing such that the incremental benefits and costs are included for those who are both positive and negative for the test.

The use of the model input population from the MIRASOL trial (which consisted of patients with high FRα expression only) limits the feasibility of conducting scenario analysis excluding the biomarker test (assessing the net clinical benefit of providing MIRV to PROC patients both with and without the biomarker). However, the commentary considered that the submission could have used sub-group data from the FORWARD-I trial presented as supportive evidence to address this.

The model did include costs related to two scenarios for FRα expression testing: at primary diagnosis of high grade ovarian, fallopian tube or primary peritoneal cancer (base case) and at platinum resistance (sensitivity analysis). Testing costs were based on the number of tests required to identify one patient with high FRα expression and a proposed testing fee of $125. Additionally, for the testing scenario at platinum resistance, the costs of archival block retrieval ($85, MBS item 72860) and rebiopsy (average cost of $50.51, based on an estimated 10% of patients receiving a rebiopsy) were applied per patient (Table 21).

Table 21: Test costs per patient applied in the economic model

Testing scenario: at primary diagnosis (base case)		**Testing scenario: at platinum resistance (sensitivity analysis)**	
Incident cases high grade ovarian cancer, serous carcinomas of the fallopian tube and primary peritoneal cancer (projected calendar year 2026)	redacted[1]	Patients with platinum-resistant high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (projected calendar year 2026)	redacted[1]
% cases with FRα testing requested (test uptake rate)	redacted%	% cases with FRα testing requested (test uptake rate)	redacted%
Number FRα tests requested	redacted[1]	Number FRα tests requested	redacted[1]
Revised number FRα tests requested	redacted[1]	Revised number FRα tests requested	redacted[1]
Patients treated with MIRV[a]	redacted[2]	Patients treated with MIRV[a]	redacted[2]
Revised patients treated with MIRV	redacted[2]	Revised patients treated with MIRV	redacted[2]
FRα tests required to identify 1 patient (Number FRα tests requested ÷ Patients treated with MIRV)	redacted	FRα tests required to identify 1 patient (Number FRα tests requested ÷ Patients treated with MIRV)	redacted
Total cost to detect one patient with FRα high expression	**$redacted (redacted x $125)**	**Total cost to detect one patient with FRα high expression**	**$redacted (redacted x $125+$85+$50.51)**

Source: Excel sheet 'Other Medical Costs' from economic workbook
FRα = folate receptor alpha; MIRV = mirvetuximab soravtansine.
[a] : Estimation of number of treated patients developed during the evaluation using data from Tables 4.2-1 – 4.2-6, p207-210 of the submission
Green font indicates updates by the applicant based on DUSC advice where 63% of ovarian cancers are assumed to be high-grade epithelial.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] <500

In the MIRASOL trial, FRα expression was undertaken using the Ventana FOLR1 (FOLR1-2.1) Assay at three central laboratories; the submission stated that this means that different laboratories and different readers were involved in the assessment of FRα expression levels used to determine patient eligibility to enrol in MIRASOL. As such, the submission stated that uncertainty resulting from inter-reader agreement being less than 100% is inherently accounted for in the economic evaluation. Additionally, the submission stated that the Ventana FOLR1 (FOLR1-2.1) Assay is anticipated to be the only TGA-approved FRα test to be approved for use in Australia. As such, the submission stated that uncertainty regarding potential differences in inter-assay performance are not applicable. The commentary considered that, although these claims may be reasonable, the limitations of the model structure meant that the impacts of false positive and false negative tests (described under Adverse events from changes to management) are not captured within the economic model.

A summary of the results of the base case economic evaluation (and the scenario analysis where FRα testing is undertaken at platinum resistance) is presented in Table 22 .

Table 22: Summary of economic evaluation results

Analyses	MIRV vs ICC			MIRV vs BEVA + ICC			Weighted ICER
	Incremental cost	Incremental QALY	ICER	Incremental cost	Incremental QALY	ICER	
Base case	**$redacted**	**0.68**	**$redacted[1]**	**$redacted**	**0.60**	**$redacted[1]**	**$redacted[1]**
Univariate analyses							
FRα testing population (base case = at primary diagnosis) • At platinum resistance	$redacted	0.68	$redacted[1]	$redacted	0.60	$redacted[1]	$redacted[1] (redacted%)

Source: Table 3.9-1, p200 and Table 3.9-2, p201 of the submission.
BEVA = bevacizumab; FRα = folate receptor alpha; ICC = investigators choice of chemotherapy; ICER = incremental cost effectiveness ratio; MIRV = mirvetuximab soravtansine; QALY = quality adjusted life year.
The redacted values correspond to the following ranges:
[1]$75,000 to < $95,000

The commentary assessed the impact of timing of FRα testing and concluded that there was a negligible impact on the incremental cost effectiveness ratio (ICER) whether FRα testing occurs at primary diagnosis or at platinum resistance.

The commentary noted that due to limitations of the model structure as described above, no further sensitivity analyses relevant for MSAC consideration could be assessed during the evaluation.

14. Financial/budgetary impacts

The submission used an epidemiological approach to estimate the expected cost to the MBS of listing the test. Consistent with the economic evaluation, the submission considered two contexts for FRα expression testing: At primary diagnosis (base case) and at development of platinum-resistance (scenario analysis). In both scenarios, testing was a one-off event (no re-testing is considered). The commentary noted that as discussed in Section 5, there is uncertainty relating to the stability of the biomarker over time.

The estimated number of tests at primary diagnosis was based on projected incident cases of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (sourced from a linear extrapolation of Australian Institute of Health and Welfare [AIHW] incidence data from 2020-2024) and assumptions of a **redacted**% test uptake rate (see Table 23).

Table 23: Estimated number of patients tested (primary diagnosis)

			Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
A	Total incident cases epithelial ovarian, fallopian tube or primary peritoneal cancer		redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
B	% cases high-grade epithelial		90%	90%	90%	90%	90%	90%
	Revised % cases high-grade epithelial		63%	63%	63%	63%	63%	63%
C	Total incident cases high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer	A x B	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
	Revised total incident cases high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer		redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
D	Test uptake rate		redacted%	redacted%	redacted%	redacted%	redacted%	redacted%
E	**Predicted number of patients tested (testing at primary diagnosis)**	**C x D**	**redacted[1]**	**redacted[1]**	**redacted[1]**	**redacted[1]**	**redacted[1]**	**redacted[1]**
	Revised predicted number of patients tested (at primary diagnosis)		**redacted[1]**	**redacted[1]**	**redacted[1]**	**redacted[1]**	**redacted[1]**	**redacted[1]**

Source: Adapted from Table 4.2-2, p208 of the submission
Revised values calculated by the department with assumption of 63% of ovarian cancers are high-grade epithelial.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000

The estimated number of tests at platinum resistance was based on the number of incident cases of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that are estimated to develop platinum-resistance following second-, third- or fourth line therapy (using proportions sourced from the literature) and assumptions of a **redacted**% test uptake rate.

The commentary noted, as this approach accounts for patients from the incident patient pool developing platinum-resistance at multiple lines of therapy, the submission did not consider prevalent patients with platinum-resistance separately. The commentary considered that the methods used by the submission result in an assumption that 138.6% of incident high grade epithelial ovarian cancer cases are expected to progress to subsequent treatments (F + I + L in Table 24 below). This approach was considered unreasonable as it may have double counted the incidence patients or underestimated the prevalent patients. As such, the predicted number of patients tested at platinum resistance is uncertain.

Table 24: Estimated number of tested patients (platinum resistance)

			Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
C	Total incident cases high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer		redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
	Revised total incident cases high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer		redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]

F	% cases advanced staged ovarian cancer initiating second-line treatment		64.1%	64.1%	64.1%	64.1%	64.1%	64.1%
G	% second-line treated with non-platinum treatment (platinum-resistant)		37%	37%	37%	37%	37%	37%
H	Patients with platinum-resistance at second-line	C x F x G	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
	Revised patients with platinum-resistance at second-line		redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
I	% cases advanced staged ovarian cancer initiating third-line treatment		44.6%	44.6%	44.6%	44.6%	44.6%	44.6%
J	% third-line treated with non-platinum treatment (platinum-resistant)		49.0%	49.0%	49.0%	49.0%	49.0%	49.0%
K	Patients with platinum-resistance at third-line	C x I x J	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
	Revised patients with platinum-resistance at third-line		redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
L	% cases advanced staged ovarian cancer initiating fourth-line treatment		29.9%	29.9%	29.9%	29.9%	29.9%	29.9%
M	% fourth-line treated with non-platinum treatment (platinum-resistant)		57.0%	57.0%	57.0%	57.0%	57.0%	57.0%
N	Patients with platinum-resistance at fourth-line	C x L x M	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
	Revised patients with platinum-resistance at fourth-line		redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
O	Total patients with platinum-resistant high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer	H + K + N	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
	Revised total patients with platinum-resistant high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer		redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
P	**Predicted number of patients tested (testing at platinum resistance)**	**O x D**	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]
	Revised predicted number of patients tested (testing at platinum resistance)		**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]	**redacted**[1]

Source: Adapted from Table 4.2-2, p208 of the submission
Revised values calculated by the department with assumption of 63% of ovarian cancers are high-grade epithelial.
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] <500

The estimated net costs of FRα expression testing (based on a proposed test cost of $125 and a patient co-payment of 80%) for both the base case (primary diagnosis) and scenario analysis (at platinum resistance) is presented in Table 25. Costs applied for the scenario analysis include additional MBS costs for archival block retrieval (all tested patients) and re-biopsy rate (applied to 10% of patients) calculated from estimates from registry data and clinical expert advice. However, the commentary noted that this was incorrectly applied by the submission (with the estimated number of re-biopsy procedures accounting to a 3.4 % re-biopsy rate). This has been corrected by the evaluation in the table below.

Table 25: Estimated use and financial implications

	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Estimated extent of use of FRα expression testing						
Number of patients tested (at primary diagnosis)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Number of patients tested (at platinum resistance)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Predicted number of patients with FRα-high tumour cell expression and platinum-resistance (eligible for treatment with MIRV)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Estimated financial implications of the FRα expression testing to the MBS (testing at primary diagnosis)						
Cost to MBS ($)	*redacted*[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Copayments (80%) ($)	*redacted*[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Cost to the MBS less copayments (80%) ($)	*redacted*[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Cost to MBS less copayments (85% copayment applied) ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Estimated financial implications of the FRα expression testing to the MBS (testing at platinum resistance)						
Cost to MBS (FRα expression testing) ($)	*redacted*[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (80%) ($)	*redacted*[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Cost to MBS (archival block retrieval*) ($)	*redacted*[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (80%) ($)	*redacted*[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Cost to MBS (re-biopsy procedure*) ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Patient copayment (80%) ($)	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]
Cost to MBS (pre-anaesthesia consultation*) ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Patient copayment (80%) ($)	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]
Cost to MBS (anaesthesia services*) ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Patient copayment (80%) ($)	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]
Total Cost to MBS ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Total Copayments (80%) ($)	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]	*redacted*[4]
Net Cost to MBS less copayments (80%) ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Net Cost to MBS less copayments (85% copayment applied) ($)	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]	*redacted*[3]
Difference in costs (testing at primary diagnosis – testing at platinum resistance) (80% copayment applied) ($)	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**
Difference in costs (85% copayment applied) ($)	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**	***redacted*[4]**

Source: Developed during the evaluation using data from Tables 4.5-3 & 4.5-4, p223-224 of the submission and sheet '7.Net changes – MBS' from the financial workbook.

FRα =Folate receptor alpha; MBS = Medicare Benefits Schedule; MIRV = mirvetuximab soravtansine.

*Archival block retrieval fee $85.00 (MBS item 72860), rebiopsy procedure (diagnostic percutaneous aspiration biopsy) fee $215.80 (MBS item 30094), pre-anaesthesia consultation fee $49.75 (MBS item 17610) and anaesthesia service fee $216.35 (MBS item 18216)

Note: Values in italics reflect those corrected during the evaluation

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] <500

[3] $0 to < $10 million

[4] net cost saving

If FRα expression testing is undertaken at primary diagnosis, it was estimated to cost the MBS **$0 to < $10 million** over 6 years (**$0 to < $10 million** when using 85% copayment), compared to a cost of **$0 to < $10 million** over 6 years (**$0 to < $10 million** with 85% copayment) if testing is undertaken at platinum resistance (a difference of **$0 to < $10 million** [or **$0 to < $10 million** with

85% copayment]).

The net financial implications for the health budget over 6 years is presented in the Table 26.

Table 26: Net financial implications for the health budget (effective price)

	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Net cost to PBS/RPBS	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Net cost to MBS - FRα expression testing at primary diagnosis	*redacted[1]*	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Net cost to MBS - FRα expression testing at platinum resistance	*redacted[1]*	*redacted[1]*	*redacted[1]*	*redacted[1]*	*redacted[1]*	*redacted[1]*
Overall net cost to health budget - FRα expression testing at primary diagnosis	***redacted[2]***	***redacted[2]***	***redacted[2]***	***redacted[2]***	***redacted[2]***	***redacted[2]***
Overall net cost to health budget - FRα expression testing at platinum resistance	***redacted[2]***	***redacted[2]***	***redacted[2]***	***redacted[2]***	***redacted[2]***	***redacted[2]***

Source: Adapted from Table 4.5-5, p225 of the submission.
FRα=folate receptor alpha; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits
Note: Values in italics represent those corrected during the evaluation
The redacted values correspond to the following ranges:
[1] $0 to < $10 million
[2] $20 million to < $30 million

The estimated net cost to the health budget over 6 years was **$100 million to < $200 million** (for FRα expression testing at primary diagnosis) and **$100 million to < $200 million** (for FRα expression testing at platinum resistance – an increase of **$0 to < $10 million** over 6 years).

The Drug Utilisation Sub-Committee (DUSC) advised the submission overestimated patient prevalence by assuming that 90% of all ovarian cancers are high-grade epithelial. DUSC clarified that approximately 70% of these are serous, resulting in a revised estimate of 63%. The department calculated the estimated use and financial implications presented in Table 27 (with proposed schedule fee at $125) and in Table 28 (with advised schedule fee of $112).

Table 27: Revised estimated use and financial implications with proposed schedule fee at $125 (calculated by the department)

	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Base case: Testing at primary diagnosis (proposed schedule fee =$125)						
Total test numbers (A)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Cost of testing to MBS (A*$125)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (A x $125 x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (80% co-payment) (B = A x $125 x 80%)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Net cost to MBS (85% co-payment) (C = A x $125 x 85%)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Scenario: Testing at platinum-resistance						
FRα expression testing (proposed schedule fee =$125)						
Total services (D)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Cost to MBS (E = D x $125)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]

Patient copayment (F = -E x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (G = E x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Archival block retrieval	MBS item 72860 (schedule fee = $85)					
Total services (D)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Cost to MBS (H = D x $85)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (I = -H x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (J = H x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Re-biopsy procedure	MBS item 30094 (schedule fee = $215.80)					
Total services (K =10% x A)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Cost to MBS (L = K x $215.80)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (M = -L x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (N = L x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Pre-anaesthesia consultation	MBS item 17610 (schedule fee = $49.75)					
Total services (K =10% x A)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Cost to MBS (O= K x $49.75)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (P = -O x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (Q = O x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Anaesthesia	MBS item 18216 (schedule fee= $216.35)					
Total services (K =10% x A)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Cost to MBS (R= K x $216.35)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (S = -R x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (T = R x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Total cost to MBS (U=E+H+L+O+R)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Total copayments (V=F+I+M+P+S)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (80% co-payment) (X = U+V)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Net cost to MBS (85% co-payment) (Y = U x 85%)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Difference 80% co-payment (Base case - Scenario) (B-X)	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**
Difference 85% copayment (Base case - Scenario) (C-Y)	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**
Difference in costs (85% copayment applied)	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**

FRα =Folate receptor alpha; MBS = Medicare Benefits Schedule; MIRV = mirvetuximab soravtansine.
*Archival block retrieval fee $85.00 (MBS item 72860), rebiopsy procedure (diagnostic percutaneous aspiration biopsy) fee $215.80 (MBS item 30094), pre-anaesthesia consultation fee $49.75 (MBS item 17610) and anaesthesia service fee $216.35 (MBS item 18216)
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] <500
[3] $0 to < $10 million
[4] net cost saving

Table 28: Revised estimated use and financial implications with advised testing cost at $112 (calculated by the department)

	Year 1 2025	Year 2 2026	Year 3 2027	Year 4 2028	Year 5 2029	Year 6 2030
Base case: Testing at primary diagnosis (advised schedule fee = $112)						
Total test numbers (A)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Cost of testing to MBS (A*$112)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (A x $112 x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (80% co-payment) (B = A x$112 x 80%)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Net cost to MBS (85% co-payment) (C = A x$112 x 85%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Scenario: Testing at platinum-resistance						
FRα expression testing (proposed schedule fee =$112)						
Total services (D)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Cost to MBS (E = D x$112)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (F = -E x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (G = E x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Archival block retrieval	MBS item 72860 (schedule fee = $85)					
Total services (D)	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]	redacted[1]
Cost to MBS (H = D x $85)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (I = -H x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (J = H x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Re-biopsy procedure	MBS item 30094 (schedule fee = $215.80)					
Total services (K =10% x A)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Cost to MBS (L = K x $215.80)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (M = -L x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (N = L x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Pre-anaesthesia consultation	MBS item 17610 (schedule fee = $49.75)					
Total services (K =10% x A)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Cost to MBS (O= K x $49.75)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (P = -O x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (Q = O x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Anaesthesia	MBS item 18216 (schedule fee= $216.35)					
Total services (K =10% x A)	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]	redacted[2]
Cost to MBS (R= K x $216.35)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Patient copayment (S = -R x 20%)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (T = R x 80%)	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]	redacted[3]
Total cost to MBS (U=E+H+L+O+R)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Total copayments (V=F+I+M+P+S)	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]	redacted[4]
Net cost to MBS (80% co-payment) (X = U+V)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**
Net cost to MBS (85% co-payment) (Y = U x 85%)	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**	**redacted[3]**

Difference 80% co-payment (Base case - Scenario) (B-X)	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**
Difference 85% copayment (Base case - Scenario) (C-Y)	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**	**redacted[4]**

Abbreviations: FRα =Folate receptor alpha; MBS = Medicare Benefits Schedule; MIRV = mirvetuximab soravtansine.
*Archival block retrieval fee $85.00 (MBS item 72860), rebiopsy procedure (diagnostic percutaneous aspiration biopsy) fee $215.80 (MBS item 30094), pre-anaesthesia consultation fee $49.75 (MBS item 17610) and anaesthesia service fee $216.35 (MBS item 18216)
The redacted values correspond to the following ranges:
[1] 500 to < 5,000
[2] <500
[3] $0 to < $10 million
[4] net cost saving

Consequently, the revised net financial implications for the health budget over 6 years of different scenarios were also calculated (Table 29).

Table 29: Financial impact and net cost analysis for 6 years (2025 to 2030) under different scenarios

Scenarios		Submission	DUSC advice	Pre-MSAC response	DUSC advice +ESC advice
FR alpha testing cost		$125	N/A	$125	$112
Number of patients tested	at primary diagnosis	redacted[1]	redacted[2]	redacted[2]	redacted[2]
	at platinum resistance	redacted[2]	redacted[3]	redacted[3]	redacted[3]
Net cost to PBS (PBS/RPBS)		redacted[4]	redacted[4]	redacted[5]	redacted[4]
Net cost to the MBS	at primary diagnosis	redacted[6]	N/A	redacted[6]	redacted[6]
	at platinum resistance	redacted[6]	N/A	redacted[6]	redacted[6]
Overall cost to health system (PBS/RPBS/MBS)	at primary diagnosis		redacted[4]	redacted[5]	redacted[4]
	at platinum resistance		redacted[4]	redacted[5]	redacted[4]
Difference in net cost to MBS between testing at primary diagnosis and at platinum resistance			**redacted[7]**	**redacted[7]**	**redacted[7]**

Abbreviations: DUSC= Drug Utilisation Sub-Committee, ESC= Evaluation Sub-Committee, FRα=folate receptor alpha; MBS = Medicare Benefits Schedule; MSAC= Medical Service Advisory Committee, PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits
Source: Calculated by the department using data from Table 25 to Table 28, DUSC advice and pre-MSAC response from the applicant (sheet '3b. Impact - proposed (pub)' in Mirvetuximab Section 4 Workbook_Pre-PBAC update).
The redacted values correspond to the following ranges:
[1] 10,000 to < 20,000
[2] 5,000 to < 10,000
[3] 500 to < 5,000
[4] $100 million to < $200 million
[5] $80 million to < $90 million
[6] $0 to < $10 million
[7] net cost saving

15. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues

- Consider a single MBS item by removing wording specifying testing at platinum resistance and testing at time of primary diagnosis, as this approach would allow for both reflexive testing at diagnosis and repeat testing post-treatment if required, particularly given the uncertainty around stability of FRα expression after treatment.
- The proportion of non-serous ovarian cancers with high FRα expression is low, therefore excluding the term 'serous' in the population description would likely have minimal impact and potentially future proof the MBS item descriptor. However, the ESCs advised that it would be preferable for the MBS test population to align with treatment eligibility for the PBS-recommended population.

Economic issues

- The use of the model input population from the MIRASOL trial limited the ability to conduct a scenario analysis excluding the biomarker test (assessing the net clinical benefit of providing MIRV to platinum-resistant ovarian cancer (PROC) patients both with and without the biomarker). However, the submission could have used sub-group data from the FORWARD-I trial (presented as supportive evidence) to address this.

Financial issues

- The submission considered two contexts for FRα expression testing: At primary diagnosis (base case) and at development of platinum-resistance (scenario analysis). The methods used by the submission for the scenario of testing at platinum resistance may have double counted incident patients or underestimated prevalent patients. As such, the predicted number of patients tested at platinum resistance (and associated costs to the MBS is uncertain.

Other issues

- The proposed MBS fee of $125.00 is high and a fee of $112.00 would align with the fee for comparable tests on the MBS.
- FRα expression by IHC is not a routine biomarker test offered by pathology laboratories in Australia for EOC patients. Laboratories do not have the necessary National Association of Testing Authorities (NATA) accreditation and a QAP for IHC testing of FRα expression has not yet been implemented by the Royal College of Pathologists Australasia (RCPA) (April 2025). No External Quality Assurance Program (EQAP) for FOLR1 testing is available through internationally accredited bodies such as EMQN, UK NEQAS, US CLIA or CAP.
- The proposed test, Ventana FOLR1 assay is not listed on the Australian Register of Therapeutic Goods (ARTG). The applicant updated in their pre-ESC response that the assessment of the Ventana FOLR1 RxDx assay was under a mutual stop clock with Therapeutic Goods Administration (TGA) until assessment of MIRV was closer to a decision by the TGA, expected in November 2025.

ESCs discussion

The Joint MSAC Evaluation Subcommittee/PBAC Economics Sub Committee (hereafter referred to as the ESCs) noted that this integrated codependent application sought Medicare Benefits Schedule (MBS) listing of an immunohistochemistry (IHC) test of folate receptor alpha (FRα) in patients with platinum resistant ovarian cancer (PROC) to determine eligibility for treatment with Pharmaceutical Benefits Scheme (PBS) subsidised mirvetuximab soravtansine (MIRV).

The ESCs noted and welcomed public consultation feedback from 2 organisations. The ESCs noted feedback was supportive of the test. The ESCs noted feedback from Rare Cancers Australia raised that the ability to identify suitable treatments based on FRα status provides patients with a greater sense of agency and clearer, more personalised treatment pathways. The ESCs noted Ovarian Cancer Australia stressed the burden of platinum-resistant cancer on patients and that testing would enable access to MIRV, reducing reliance on chemotherapy, and supporting efficient resource use. The ESCs further noted comments from Ovarian Cancer Australia that without access to new therapies, patients rely on clinical trials, self-funding costly tests and medications, or enduring multiple lines of chemotherapy with significant side effects and limited benefit. Ovarian Cancer Australia also raised the importance of timely testing at appropriate treatment stages to avoid missed opportunities, noting that tumour testing at recurrence is not yet standard practice.

The ESCs noted that the commercial VENTANA FOLR1 (FOLR1-2.1) RxDx Assay had received regulatory approval from the U.S. Food and Drug Administration (FDA) and CE (Conformité Européene, or European Conformity) marking in the European Union. However, it has not yet been approved by the Therapeutic Goods Administration (TGA) in Australia or listed on the Australian Register of Therapeutic Goods (ARTG). The ESCs further noted that the assessment of Ventana FOLR1 RxDx assay was under a mutual stop clock with TGA until assessment of MIRV was closer to a decision by the TGA and the consideration of the test will be in parallel with the decision of MIRV. The ESCs noted that at the time of consideration, no External Quality Assurance Program (EQAP) for Ventana FOLR1 testing was available through international programs such as the European Molecular Genetics Quality Network (EMQN), United Kingdom National External Quality Assessment Service (UK NEQAS), United States Clinical Laboratory Improvement Amendments (US CLIA) or College of American Pathologists (CAP). Furthermore, the ESCs noted that no diagnostic laboratories in Australia are currently offering Ventana FOLR1 testing. The ESCs acknowledged the applicant's pre-ESC response, which provided a rationale for the use of a globally approved platform (Ventana FOLR1 RxDx) for FRα IHC testing. Additionally, the ESCs noted the applicant stated that it was liaising with the Royal College of Pathologists of Australasia (RCPA) to establish a Quality Assurance Program (QAP).

The ESCs noted the population, intervention, comparator, outcomes (PICO) and the clinical management algorithm. The ESCs noted that key trials excluded patients with non-serous histology and platinum-refractory disease (progression at <3 months). The ESCs noted the proportion of non-serous ovarian cancers with high FRα expression is low, therefore excluding the term 'serous' in the population description would likely have minimal impact and would potentially future proof the MBS item descriptor. However, the ESCs also emphasised that the codependent FRα IHC test should identify patients most likely to benefit from accessing the relevant treatment on the PBS. Therefore, the ESCs advised that it would be preferable for the MBS test population to align with treatment eligibility for the PBS-recommended population.

The ESCs considered that the testing should not be limited to the platinum resistance stage because the ESCs considered FRα expression appeared to remain stable. The ESCs noted platinum resistance would be included in the PBS restriction for the drug. The ESCs agreed the MBS item descriptor should be restricted to be requested by specialist or consultant physicians and that it should be pathologist determinable. The ESCs suggested considering a single MBS item descriptor (Table 30) by removing wording specifying testing at platinum resistance and testing at time of primary diagnosis, as this approach would allow for both reflexive testing at diagnosis and repeat testing post-treatment if clinically necessary, particularly given the uncertainty around the stability of FRα expression after treatment. The ESCs also noted that delaying testing until resistance or non-response could significantly delay access to treatment for high-risk patients.

The ESCs considered that the proposed MBS fee of $125.00 was high and a fee of $112.00 would be appropriate as it would align with the fee for comparable tests on the MBS that use a similar methodology in processing, staining and scoring of such specimens.

The ESCs noted that the Ventana platform is commonly used in Australian laboratories and it demonstrated robust analytical performance including high sensitivity, specificity, and

reproducibility across reagent lots, instruments, days, laboratory sites, and readers if the test is carried out by pathologists trained in semi-quantitative IHC interpretation. The ESCs noted that the inherent subjectivity of semi-quantitative IHC remains a limitation. The ESCs noted good concordance of the test with positive predictive value (PPV) of 96.4% (submission) or 85.1% (assessor adjusted) and negative predictive value (NPV) of 97.92% (submission) or 97.15% (assessor adjusted). The ESCs considered the test failure rate at 1.6% was low.

The ESCs acknowledged the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Instruction for Use (IFU)[11] recommends re-reading of the slide by a second pathologist and agreed with the applicant's pre-ESC response that borderline results should be reviewed by a second pathologist. However, the ESCs suggested a local validation is required to assess inter-laboratory reproducibility, concordance, and overall reliability of the FRα IHC assay within Australian pathology laboratories.

The ESCs noted limited evidence in demonstrating the stability of FRα in archived formalin-fixed paraffin-embedded (FFPE) tissue blocks or tissue microarrays (TMAs) and the stability of FRα expression in disease progression or treatment. However, the ESCs noted recently reported data at a conference[12] showed high consistency (86%) of FRα IHC status across biopsies taken at different times. The ESCs suggested further research was needed to determine the reliability of archival tissue versus fresh biopsies for FRα IHC testing.

The ESCs noted that the cut-off threshold for high FRα expression (≥75%, PS2+) was selected based on trial data which showed minimal or no response to MIRV in patients with low or medium FRα expression. The ESCs acknowledged the applicant's selection of threshold for high FRα expression was supported by multiple clinical trials, including MIRASOL, SORAYA, and FORWARD-I. However, the ESCs considered there was a high risk of bias in the selection of the binary cut-off threshold due to a retrospective design, subjectivity inherent in IHC testing, and lack of blinding in the trial. The ESCs therefore considered future studies may explore alternative thresholds and continuous scoring models to refine patient selection.

The ESCs considered that there was no consistent evidence to support FRα expression as a prognostic marker for survival outcomes (overall survival [OS] or progress-free survival [PFS]). Therefore, FRα expression alone is not considered to have prognostic value. The ESCs acknowledged the applicant's claim of codependency and biomarker validity. The applicant stated that there is a strong biological rationale and clinical trial evidence supports FRα as a predictive biomarker for MIRV efficacy. The ESCs noted the applicant also argued that although FRα is not a variant-based biomarker, its expression-based predictive value is well-supported by the evidence.

The ESCs noted the clinical claims that FRα expression status testing and MIRV results in superior health outcomes compared to no testing and standard of care therapy (non-platinum chemotherapy). The ESCs noted the submission presented direct evidence from the MIRASOL trial comparing MIRV to investigator's choice chemotherapy (ICC) in the target population—patients with FRα-high expression epithelial ovarian cancer (EOC) who are platinum-resistant. In addition, the submission used a linked evidence approach to support the use of the MIRV and FRα-high expression test combination. This approach included additional studies of the biomarker and test performance.

Regarding the clinical effectiveness, the ESCs acknowledged the predictive value of FRα expression testing, noting it is associated with clinically meaningful treatment benefits from MIRV treatment in patients with a high FRα expression (≥75%, PS2+). The ESCs agreed that positive health outcomes in FRα-high patients are expected but noted patients with medium FRα expression had worse outcomes on MIRV compared with ICC, indicating no benefit in this subgroup. The ESCs further noted the submission did not present evidence for FRα negative patients.

[11] https://elabdoc-prod.roche.com/eLD/api/downloads/625da298-2641-ee11-2091-005056a71a5d?countryIsoCode=XG
[12] https://meetings.asco.org/abstracts-presentations/253565

The ESCs considered the evidence was broadly applicable to the intended target population and clinical setting in Australia. This was especially relevant for patients with platinum-resistant high-grade serous epithelial ovarian cancer (EOC) exhibiting a high FRα expression, aligning with the proposed use of the FRα test and MIRV treatment.

The ESCs noted, at the time, FRα testing was not performed in standard clinical practice. While FRα IHC testing did not pose any additional safety concerns, a positive test result would bring a change in clinical management for a patient by introducing an additional treatment option for patients who experience resistance or no-response to existing therapies.

Regarding the safety of the test, the ESCs noted that FRα IHC testing is considered low risk, particularly when performed reflexively at diagnosis or using archived diagnostic tissue. The ESCs noted that testing reflexively at diagnosis will reduce treatment delays. The ESCs agreed with the applicant's pre-ESC response that the inherent risks of rebiopsy procedures are manageable and most patients would not require a rebiopsy.

The ESCs noted that the economic model did not incorporate diagnostic test performance parameters beyond the inclusion of testing costs. Therefore, the negative clinical and economic outcomes of false positive (FP) or false negative (FN) results were not assessed in the model. Furthermore, the ESCs noted that, based on the evaluation's estimates testing 100 patients in the Australian target population would result in approximately 15FN and 3FP. The ESCs considered that patients receiving false positive results may be exposed to MIRV treatment without deriving benefit and may potentially experience worse outcomes than if they had received standard non-platinum chemotherapy. The ESCs considered the applicant's pre-ESC response regarding the inaccuracies associated with false negatives and false positives were already captured within the clinical trials was appropriate. However, the ESCs highlighted that although the targeted population in the Australian setting is the same as in the clinical trial, test accuracy in the Australian setting might be different as no local validation data were available.

The ESCs noted the use of the MIRASOL trial population in the economic evaluation limited the ability to model a scenario analysis to include the biomarker negative population for assessing the net clinical benefit of providing MIRV to platinum-resistant ovarian cancer (PROC) patients both with and without the biomarker. The ESCs agreed with the commentary that the submission could have used sub-group data from the FORWARD-I trial as supportive evidence to address this issue.

The ESCs noted that the economic model included costs related to two scenarios for FRα expression testing, one at primary diagnosis of high grade ovarian, fallopian tube or primary peritoneal cancer (base case), and one at platinum resistance (sensitivity analysis). Test costs were based on the number of tests required to identify one patient with high FRα expression and the applicant proposed testing fee of $125.

The ESCs noted that the additional cost of archival block retrieval ($85, MBS item 72860[13]) and rebiopsy (average cost of $50.51, based on an estimated 10% of patients receiving a rebiopsy) were applied per patient for the testing scenario at platinum resistance. Although these additional costs had minimal impact (<1%) on the incremental cost-effectiveness ratio (ICER), there was a slight increase in overall financial costs due to the additional MBS items required to support testing.

The ESCs noted the overall net costs to the health budget for FRα expression testing at diagnosis and at platinum resistance. The ESCs noted that the methods used by the submission resulted in an assumption that 138.6% of incident high grade epithelial ovarian cancer cases were expected to progress to subsequent treatments. However, the ESCs considered this approach was unreasonable as it may have double counted the incidence patients or underestimated the prevalent patients. Furthermore, the ESCs noted that the estimated proportions of patients

[13] https://www9.health.gov.au/mbs/search.cfm?q=72860&Submit=&sopt=S

developing platinum resistance may include patients who are platinum refractory. Since there was no clinical evidence presented for the benefit of MIRV for this patient population, the inclusion of these patients would impose a risk of leakage. Therefore, the ESCs considered the predicted number of patients tested at platinum resistance was uncertain leading to uncertainty around the financial impact of the test.

Table 30 MBS item descriptor suggested by the Evaluation Sub-Committees (ESCs)

Category 6 – Pathology Services
MBS item XXXX A test of tumour tissue using immunohistochemistry for the detection of membrane FRα tumour expression status, requested by a specialist or consultant physician, if the test is: • in a patient with high-grade serous epithelial ovarian, fallopian tube or primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer; and • to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme. (See PN.1.2 of explanatory notes to this Category)
Fee: $112.00 Benefit: 75% = $84.00; 85% = $95.20

Abbreviations: FRα = folate receptor alpha

16. Applicant comments on MSAC's Public Summary Document

AbbVie welcomes MSAC's acknowledgement of the significant unmet need faced by patients with platinum-resistant ovarian cancer, and its commitment to supporting timely access to innovative therapies. We remain dedicated to working collaboratively with government stakeholders, clinicians, and the patient community to ensure prompt access to this much-needed new treatment option.

17. Further information on MSAC

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